"Predictors of Drug Induced Liver Injury (DILI) among patients receiving anti-tubercular therapy"

Thesis submitted to the faculty of

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

for the award of the degree of MD in the subject of General Medicine

by

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AIIMS, Bhopal Institutional Human Ethics Committee- Student Research (IHEC-SR) in its 7th meeting held on 22nd February 2023 discussed your proposal titled **"Predictors of Drug Induced Liver Injury (DILI) among patients receiving anti-tubercular therapy"** and evaluated it for suitability for your dissertation as required for fulfilment of MD/MS program.

Following members attended the meeting:

1. Prof. D. K. Pal, Former HoD Community Medicine, GMC, Bhopal.....Chairperson
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The decision of the committee is as follows:

The AIIMS, Bhopal IHEC-SR approves your research protocol. All research related activities must begin only after the date of this approval. The validity of this approval is till two years from the date of issuance. Please submit a closure report / renewal request before expiration of the validity for this approval.

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List of Abbreviations

1. TB - Tuberculosis

2. YLL - Years of Life Lost

3. DALY - Disability-Adjusted Life Year

4. HIV - Human Immunodeficiency Virus

5. MDR-TB - Multidrug-Resistant Tuberculosis

6. ARTI - Annual Risk of Tuberculosis Infection

7. RNTCP - Revised National Tuberculosis Control Program

8. CBNAAT - Cartridge-Based Nucleic Acid Amplification Test

9. DST - Drug Susceptibility Testing

10. DILI - Drug-Induced Liver Injury

11. DOTS - Directly Observed Treatment, Short-Course

12. INH - Isoniazid

13. PZA - Pyrazinamide

14. RMP - Rifampicin

15. STDC - State Tuberculosis Demonstration Centre

16. PMDT - Programmatic Management of Drug-Resistant Tuberculosis

17. HLA - Human Leukocyte Antigen

18. CTCAE - Common Terminology Criteria for Adverse Events

19. ALT - Alanine Aminotransferase

20. AST - Aspartate Aminotransferase

21. ALP - Alkaline Phosphatase

22. GGT - Gamma-Glutamyl Transferase

23. ULN - Upper Limit of Normal

24. NRTI - Nucleoside Reverse Transcriptase Inhibitor

25. NSAID - Non-Steroidal Anti-Inflammatory Drug

26. RUCAM - Roussel Uclaf Causality Assessment Method

27. HBV - Hepatitis B Virus

28. AUC - Area Under the Curve

29. IQR - Interquartile Range

30. INR - International Normalized Ratio

31. BMI - Body Mass Index

32. ART - Antiretroviral Therapy

33. NAT2 - N-acetyltransferase 2

34. aHR - Adjusted Hazard Ratio

35. AFB - Acid-Fast Bacillus

36. GSTM - Glutathione S-Transferase Mu

37. GSTT - Glutathione S-Transferase Theta

38. CP - Continuation Phase (of ATT)

39. IP - Intensive Phase (of ATT)

40. WHO - World Health Organization

41. MandV - Maria and Victorino

42. DDW-J - Digestive Disease Week Japan

43. WHO-UMC - World Health Organization-Uppsala Monitoring Centre

44. CAM - Complementary and Alternative Medicine

45. MELD - Model for End-Stage Liver Disease

46. ATS - American Thoracic Society

47. BTS - British Thoracic Society

48. LFT - Liver Function Tests

49. RFT - Renal Function Tests

50. CBC - Complete Blood Count

51. DIH - Drug-Induced Hepatotoxicity

52. MAC – Mid Arm Circumference

53. OR - Odds Ratio

54. DCA - Decision Curve Analysis

55. GST - Glutathione S-Transferase

56. CI - Confidence Interval

57. CKD - Chronic Kidney Disease

58. AE - Adverse Event

59. NLR - Neutrophil-to-Lymphocyte Ratio

60. PLR - Platelet-to-Lymphocyte Ratio

61. SII - Systemic Immune-Inflammation Index

62. TLC - Total Leukocyte Count

63. PTB - Pulmonary Tuberculosis

64. EPTB - Extrapulmonary Tuberculosis

65. OPD - Outpatient Department

66. IPD - Inpatient Department

67. ADR - Adverse Drug Reaction

68. MRI - Magnetic Resonance Imaging

69. USG - Ultrasonography

70. CT - Computed Tomography

71. ELISA - Enzyme-Linked Immunosorbent Assay

72. HCV - Hepatitis C Virus

73. ADA - Adenosine Deaminase

74. ICTC - Integrated Counselling and Testing Centre

75. APL - Above Poverty Line

76. BPL - Below Poverty Line

77. CLD - Chronic Liver Disease

78. AIC - Akaike Information Criterion

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Introduction

Introduction:

According to Annual Reports – Central Tuberculosis Division, India continues to bear the highest tuberculosis (TB) burden globally. In 2015, the estimated TB incidence ranged from 217 to 355 cases per 100,000 population, with mortality estimates ranging from 26 to 35 deaths per 100,000 population. These figures remained relatively stable in 2016, with incidence estimates again ranging from 217 to 345 cases per 100,000 and mortality estimates holding at 26 to 35 deaths per 100,000 population. In 2017, the TB incidence estimate remained consistent, ranging from 217 to 345 cases per 100,000 population, while mortality showed a slight decrease, with estimates ranging from 25 to 34 deaths per 100,000 population. The data for 2018 showed an increase in incidence estimates, ranging from 238 to 265 cases per 100,000 population, while mortality estimates ranged from 20 to 29 deaths per 100,000 population, indicating a possible slight improvement in TB-related mortality. The year 2019 saw a further decline in TB incidence estimates, which ranged from 224 to 253 cases per 100,000 population, and mortality estimates ranging from 20 to 28 deaths per 100,000 population. The data for 2020, 2021, and 2022 is less complete, with some gaps in the incidence figures, but the general trend appears to reflect ongoing efforts to reduce both TB incidence and mortality in the country over time.(1)

As per the National Strategic Plan 2017-2025 for TB Elimination in India – Central Tuberculosis Division, TB mortality is alarmingly high, with 480,000 deaths in 2015 (CI: 380,000-590,000), making TB the third leading cause of years of life lost (YLLs) in the country. TB contributes to 3.3% of Disability-Adjusted Life Years (DALYs) due to all-cause premature mortality and morbidity in India. India's TB epidemic is not homogeneous; it exhibits significant regional variations influenced by factors such as HIV prevalence and the quality of healthcare infrastructure. Approximately 5% of incident TB cases are co-morbid with HIV, although this proportion varies depending on the HIV

prevalence in different regions. Data from seven subnational prevalence surveys and district-level infection surveys, along with program notification data on TB, MDR-TB, and TB/HIV, reveal that the country's TB epidemiology ranges from very high to very low TB prevalence, depending on the state or region. There is also a distinct difference between urban and rural areas, with urban regions typically having lower TB prevalence but higher Annual Risk of TB Infection (ARTI), while rural areas exhibit higher prevalence but lower ARTI. The Revised National Tuberculosis Control Program (RNTCP) has been a key player in addressing this burden. Since 2007-08, RNTCP has screened approximately 20 million symptomatic individuals annually using microscopy, leading to the initiation of TB treatment in about 1.5 million people annually. The introduction of rapid molecular diagnostics, such as the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) and Line Probe Assay in 2009, and their subsequent scale-up from 2012 onwards, have significantly enhanced TB detection across the country. In 2016 alone, 520,000 patients were tested using these methods, identifying 35,000 Rifampicin-resistant or multidrug-resistant TB (MDR-TB) cases. Furthermore, second-line drug susceptibility testing (DST) using liquid culture systems has been implemented and is being scaled up nationwide, with full coverage anticipated by December 2017. Despite these efforts, India's TB burden remains disproportionately high relative to its population, and recent evidence suggests that while the burden may be reducing, the decline is very slow. The wide geographical variation in TB epidemiology and trends underscores the need for tailored approaches to TB control in different regions. Challenges such as delayed diagnosis, inadequate treatment, high rates of recurrent TB, drug resistance, diabetes, HIV, undernutrition, and rapid urbanization continue to drive the TB epidemic in India. Additionally, inadequate data and surveillance systems, particularly concerning privately treated patients, hide severe local epidemics and impede

effective TB control. The diversity of TB epidemiology in India necessitates the adoption of different strategies to address the problem effectively across various regions. (2)

Antituberculosis (ATT) drug-induced liver injury (DILI) is a significant and potentially severe adverse effect associated with the treatment of tuberculosis (TB). A retrospective study aimed to assess the prevalence of DILI among patients undergoing anti-TB therapy and to examine some of the known risk factors contributing to the development of DILI. The Directly Observed Treatment Short Course (DOTS), a cornerstone of the Revised National Tuberculosis Control Programme (RNTCP) in India, utilizes isoniazid (INH), pyrazinamide (PZA), and rifampicin (RMP) as its primary drugs, all of which are known for their hepatotoxic potential and can lead to DILI. Although ethambutol and streptomycin are also part of the DOTS regimen, they are associated with different adverse effects that do not typically include DILI. DILI caused by ATT drugs presents a major challenge, as it not only complicates TB treatment but also significantly increases morbidity and mortality among affected patients. The severity of hepatotoxicity can range from a mild, transient rise in liver enzymes to acute liver failure, and in some cases, even death. Studies indicate that the mortality rate following the development of jaundice due to DILI ranges from 4% to 12%. Notably, the prevalence of DILI varies widely across different countries, with reported rates ranging from 2% to 39%. Several factors contribute to the higher prevalence of DILI in developing countries, including the presence of acute or chronic liver disease, alcoholism, malnutrition, indiscriminate drug use, advanced stages of TB, and other coexisting chronic illnesses. INH and RMP are known to cause DILI through diverse mechanisms. For instance, a meta-analysis revealed that RMP, when used in combination with other drugs in a multidrug regimen, increased the prevalence of DILI from 1.6% to 2.55% in adults. PZA has also been identified as a significant risk factor for liver injury. The reported prevalence of DILI in anti-TB

chemotherapy, particularly involving INH, RMP, and PZA, ranges from 0.6% to 3%. Among all first-line ATT agents, PZA is considered the most common cause of DILI. As per Saha et al., an Analysis of pooled data from four prospective Indian studies conducted within the DOTS framework found the risk of DILI to be as high as 11.5%, whereas a meta-analysis of 14 studies from Western countries reported a lower risk of 4.28%.(3) At the State level, the State TB Demonstration Centre (STDC) is bolstered by various support mechanisms to ensure comprehensive TB management and control. The State TB Forums are instrumental in community engagement, while the State-level Programmatic Management of Drug-resistant TB (PMDT) committees provide guidance and oversee the implementation of PMDT. Additionally, the State-level Technical Working Group for HIV-TB plays a crucial role in ensuring effective coordination between TB and HIV programs. Nodal DR-TB centres have been established for managing drug-resistant TB under the PMDT, including the use of newer drugs and monitoring adverse drug reactions (ADR). These centres also serve as referral units for complex cases. To maintain the quality of care, it is vital to promptly identify and report adverse events during TB treatment. This allows for timely management and minimizes the impact on patients. In this regard, an adverse event module has been integrated into Nikshay, the national digital platform, enabling comprehensive management of adverse events from reporting to outcome declaration.

In 2021, technical guidance for a comprehensive package for Differentiated Care of TB patients was introduced. This approach is crucial for reducing morbidity and preventable mortality among TB patients by implementing a holistic care package at various health facilities across India. The focus is on clinical care, including the assessment of basic clinical parameters such as vitals, general conditions, nutritional status, and routine investigations. This allows for the early identification of patients with severe disease or

those at risk of adverse effects. Timely referral of high-risk TB patients, identified through symptoms and signs, to hospital-based care, when necessary, is expected to reduce TB-related mortality. To ensure systematic monitoring, the recording and reporting of Differentiated Care of TB patients are now available on Nikshay for States and Union Territories (UTs). This digital system also includes a feature for managing drug inventories. Suppose a patient returns drugs due to death, wrong dispensation, loss to follow-up, or an adverse drug reaction. In that case, the returned quantity is immediately added back to the drug inventory in Nikshay, making it available for dispensing to another patient. In 2022, the Nikshay platform saw significant enhancements, including the addition of 15 new reports, 5 registers, and 8 data entry modules covering various thematic areas such as drug dispensation, adverse drug reactions, and contact tracing. PMDT reports were also revamped to include new concepts like case finding, case holding, and treatment outcome reports. This continuous improvement in the Nikshay ecosystem ensures that the increasing volume of data is efficiently processed and utilized for better TB management across the country. (1)

Several studies have investigated the potential risk factors for drug-induced liver injury (DILI) in patients undergoing tuberculosis (TB) treatment, revealing the complexity of mechanisms underlying DILI. Although TB treatment often involves combinatorial regimens with various antibiotics, the potential association between these regimens and the development of DILI has not been thoroughly explored. While novel urinary and blood biomarkers identified through high-throughput methods like mass spectrometry or sequencing show potential for predicting DILI, their application in clinical practice remains limited due to uncertainty and high costs. Routine laboratory examinations used in TB diagnosis may offer objective and quantitative parameters to screen for DILI-related risk factors. Ji S et al concluded that prediction models could play a crucial role

in identifying significant risk factors in real-world settings, which are essential for accurate diagnosis, effective treatment, and improved prognosis.(4)

Many risk factors for tuberculosis drug-induced liver injury (TB-DILI) have been identified, including patient age, chronic liver disease, malnutrition, hepatitis B, hepatitis C, excessive alcohol consumption, HIV, extra-pulmonary TB, polymorphisms in Cytochrome P450 enzymes (particularly 2E1), slow acetylator status, certain HLA phenotypes, and Asian ethnicity. Additionally, elevated pre-treatment aminotransferase levels and low pre-treatment albumin levels have been reported as independent risk factors for TB-DILI. Despite these known associations, approaches based on risk factors to predict the occurrence of TB-DILI before the initiation of anti-tuberculosis therapy (ATT) have performed poorly. As per Patterson B et al, targeting only specific risk groups for liver test (LT) monitoring, as recommended by the American Thoracic Society, may not be sufficient to minimize harm from TB-DILI. In the absence of reliable pre-treatment risk stratification, routine monitoring strategies have been advocated. Although the optimal timing for such monitoring is yet to be established, some investigators suggest conducting liver tests two weeks after the initiation of ATT, corresponding to the median time of TB-DILI onset. The hypothesis is that early identification of subclinical TB-DILI, leading to earlier cessation of ATT, may prevent acute liver failure in some cases. Additionally, early detection of mild TB-DILI cases could allow for shorter interruptions in ATT, enabling quicker normalization of alanine aminotransferase (ALT) or bilirubin levels. (5)

DILI can lead to severe hepatic complications, potentially necessitating the discontinuation or alteration of ATT, which poses a risk of treatment failure, drug resistance, and increased morbidity and mortality. Despite the known association between ATT and DILI, current screening and prevention strategies for this complication remain

inadequate due to a lack of definitive and consistent predictive markers. The existing literature on predictors of ATT-induced DILI presents conflicting findings, with various studies suggesting different risk factors such as age, sex, genetic predisposition, nutritional status, comorbidities (e.g., HIV, diabetes), and specific drug regimens. However, these predictors vary across populations and study designs, with some results even being contradictory. For instance, while certain studies highlight advanced age as a risk factor, others fail to establish a clear correlation. These inconsistencies limit current evidence's generalizability and clinical applicability, resulting in an unmet need for a reliable, evidence-based screening approach. Identifying robust and consistent predictors of ATT-induced DILI is crucial for developing preventive strategies and improving patient outcomes. A study addressing the gaps and contradictions in the existing literature will help clinicians identify patients at higher risk for DILI. Early identification of at-risk individuals could allow for pre-emptive monitoring, dose adjustments, or modifications in treatment regimens, thereby reducing the incidence and severity of hepatotoxicity. This is particularly important given the absence of formal guidelines for screening patients undergoing ATT for DILI risk. The proposed study will contribute to filling this critical gap by evaluating potential predictors across a diverse population. Such a study has the potential to inform clinical guidelines and provide a foundation for personalised treatment approaches in patients receiving ATT. By improving early detection and prevention of DILI, we can ultimately enhance patient safety, ensure the continuity of effective TB treatment, and reduce the burden of liver-related complications.

Review of Literature

Review of literature:

Drug-Induced Liver Injury (DILI) is a significant cause of acute liver failure, with a fatality rate reaching up to 50%. Mahmood K et al reported the incidence of ATT-induced hepatoxicity from Asia to be around 19.8%(6) and Steele MA et al reported that the incidence of ATT-induced DILI from the west was 4.3%. (7) Hosack T et al described the classification of DILI into two categories: intrinsic and idiosyncratic DILI. Intrinsic DILI is dose-dependent, predictable, and typically manifests within hours to days of drug exposure. It is often associated with lipophilic drugs, which easily cross the hepatocyte lipid bilayer and undergo biotransformation into reactive metabolites. These metabolites induce oxidative stress, disrupt mitochondrial function, and alter bile acid homeostasis, leading to liver damage. Paracetamol is the most well-known drug causing intrinsic DILI, with other examples including amiodarone, valproic acid, and statins. On the other hand, idiosyncratic DILI is unpredictable, with a variable onset ranging from weeks to months. The severity of idiosyncratic DILI can vary significantly, from spontaneous recovery after drug cessation to cases of acute liver failure requiring hospitalization, liver transplantation, or even resulting in death. The pathogenesis of idiosyncratic DILI is thought to involve the adaptive immune system, with specific HLA types playing a critical role in genetically predisposed individuals. Based on liver enzyme profiles, idiosyncratic DILI can present in hepatocellular, cholestatic, or mixed forms. Idiosyncratic DILI can be further subdivided into immune-mediated and non-immune-mediated reactions. Immune-mediated idiosyncratic DILI typically presents within 1–6 weeks of drug administration and is characterized by symptoms like fever, rash, eosinophilia, and the presence of autoantibodies, with severe cases potentially leading to Stevens-Johnson syndrome. Non-immune-mediated idiosyncratic DILI, in contrast, has a delayed onset and does not exhibit these immune-related features.

The Common Terminology Criteria for Adverse Events (CTCAE) provides a framework for grading the severity of liver enzyme elevations in DILI, with Grade 1 defined as ALT/AST levels greater than the upper limit of normal (ULN) to 3 times ULN, Grade 2 as 3–5 times ULN, Grade 3 as 5–20 times ULN, and Grade 4 as greater than 20 times ULN. (8)

As described by Brennan PN et al, Drug-Induced Liver Injury (DILI) can be classified based on liver enzyme derangement into several clinical phenotypes. Idiosyncratic DILI can present in hepatocellular, cholestatic, mixed, or chronic forms. In hepatocellular injury, alanine transaminase (ALT) is elevated less than fivefold above the upper limit of normal (ULN) or with a ratio (R) greater than 5. The cholestatic injury occurs when alkaline phosphatase (ALP) is elevated less than twofold above ULN or with an $R \leq 2$, while mixed injury has an R between 2 and 5. Chronic DILI presents acutely but shows evidence of persistent liver injury beyond one year. Commonly implicated agents in idiosyncratic DILI include antimicrobials, anticonvulsants, antiarrhythmics, androgens, oestrogens/progesterone, immunomodulatory drugs, and antineoplastics. Another phenotype is drug reaction with eosinophilia and systemic symptoms, characterized by drug-related hypersensitivity involving eosinophilia and systemic inflammation, often triggered by anticonvulsants and nucleoside reverse transcriptase inhibitors (NRTIs). Drug-induced autoimmune hepatitis mimics autoimmune hepatitis, with serological and histological evidence, and is commonly caused by non-steroidal anti-inflammatory drugs (NSAIDs), statins, minocycline, and nitrofurantoin. Secondary sclerosing cholangitis presents as acute DILI with histological or radiological signs of sclerosing cholangitis, frequently linked to inhalational anaesthetics, atorvastatin, and 6-mercaptopurine. Granulomatous hepatitis, marked by granuloma formation on histology, is often caused by anticonvulsants and sulphonamides. Acute fatty liver results from microvesicular

steatohepatitis, typically induced by reverse transcriptase inhibitors. Drug-associated fatty liver disease is consistent with non-alcoholic fatty liver disease (NAFLD) and can be attributed to agents such as methotrexate, corticosteroids, and 5-fluorouracil. Nodular regenerative hyperplasia, characterized by diffuse nodularity around central hepatocytes, is commonly associated with antineoplastic or cytotoxic drugs. Ductopenia involves chronic cholestasis and ductular loss and is frequently linked to antimicrobials, including β-lactams, tetracyclines, and sulphonamides. Lastly, liver tumours, such as hepatocellular adenoma or carcinoma, can arise due to the use of anabolic androgenic steroids or oral contraceptives, which are known to induce neoplastic changes. This classification framework organizes DILI into distinct clinical phenotypes based on the underlying enzyme derangements and links them to commonly implicated drugs. (9)

Drug-induced liver injury (DILI) secondary to anti-tuberculous treatment (ATT) is a potentially fatal complication, occurring in 2-28% of patients depending on the population, regimen, and definition used. Risk factors include co-infections (HIV, hepatitis B/C), chronic liver disease, alcohol consumption, malnutrition, older age, female sex, and slow acetylator status. There is no universally accepted definition for TB DILI, though most guidelines focus on ALT levels. The DILI Expert Working Group and other studies suggest ALT and ALP criteria for diagnosis, with thresholds for cessation of ATT at ALT >5x upper limit of normal (ULN) or at ALT 3-5xULN with symptoms like jaundice or nausea. A key challenge is differentiating between true DILI and liver adaptation due to TB infection. Symptom screening and risk factors are crucial in identifying DILI early. Monitoring liver tests during ATT is recommended by various guidelines, with some advocating universal testing and others risk-based monitoring. Causality can be assessed using tools like the RUCAM score. Abbara A et al conducted a study at Northwick Park Hospital in which, 6.9% of 1529 TB patients developed DILI.

Many cases involved stopping ATT, but a significant number resolved without stopping treatment. Treatment reintroduction was successful in most patients, often following a sequential dose re-escalation strategy. Importantly, the study identified alcohol consumption, higher drug doses (isoniazid and pyrazinamide), and lower body weight as factors increasing the risk of DILI. Despite careful management, some cases led to liver failure, particularly in vulnerable populations such as those co-infected with HIV. Mortality associated with DILI in the study was 4.8%. (10)

Indian patients appear to have a higher risk of ATT-induced hepatotoxicity, with a reported incidence of 11.5% compared to 4.3% in Western studies. A study by Anand A et al involving 152 Indian patients found that chronic HBV infection significantly increased the risk of liver dysfunction in those on ATT, with a 37.5% incidence compared to 10.2% in HBV-negative patients. Patients with HBV who developed liver dysfunction were older and had more severe liver injury. Hepatotoxicity was also higher in patients receiving empirical ATT. A second part of the study evaluated 69 patients with ATT-induced liver dysfunction. The majority (68.1%) presented with jaundice, while 31.8% had prodromal symptoms without jaundice. Serious complications included hepatic encephalopathy and fulminant hepatic failure, with higher mortality among older patients and those who experienced delayed recognition of hepatitis. Fatal complications were more common in those who had received ATT for longer periods and in patients with higher serum bilirubin levels. Reintroduction of ATT was attempted in 49 patients, with high success rates for isoniazid (96%) and rifampicin (88%). However, pyrazinamide reintroduction was less successful, and the recurrence of hepatotoxicity prevented reintroduction in some cases. (11)

Ji S et al investigated the risk factors for developing drug-induced liver injury (DILI) in 1,979 patients undergoing anti-TB treatment, identifying key predictors and creating a predictive model. Of the initial 4,715 patients, many were excluded due to missing liver function tests or the presence of baseline liver conditions, such as hepatitis B or C and fatty liver. Ultimately, 83 patients (4.2%) developed DILI within 180 days of treatment. Through logistic regression, five significant risk factors were identified: age, elevated total bilirubin, neutrophil count, alcohol consumption, and uric acid levels. Age, elevated total bilirubin, neutrophil count, and alcohol consumption were found to increase the risk of DILI, while higher uric acid levels appeared to have a protective effect. A predictive model based on these factors demonstrated good performance, with an Area Under the Curve (AUC) of 0.833, sensitivity of 0.759, and specificity of 0.805 in the training group. The model's accuracy was validated on two independent groups, showing moderate discrimination with AUCs of 0.668 and 0.753, respectively. (4)

In a study by Patterson B et al,1247 cases of active tuberculosis were enrolled between January 2015 and December 2018. Among these, 103 cases (8.3%) of confirmed TB-DILI were reported. Furthermore, 41.7% of these cases were diagnosed within two weeks of initiating treatment, while the remaining 58.3% occurred afterwards. The median time from treatment initiation to TB-DILI was 19 days (IQR: 8 to 54 days). Factors like patient age, pre-treatment INR, and platelet count showed associations with TB-DILI, although with small effect sizes. A significant association was found for ALT levels, where every 30 U/L increment in ALT pre-treatment led to a 1.4-fold increased risk of developing TB-DILI. After two weeks of treatment, changes in ALT levels, alongside age and platelet count, were strongly associated with TB-DILI risk. An increase of 30 U/L in ALT resulted in a 2-fold increased risk for late DILI, with an AUROC value of 0.70 for predictive models. (5)

Puri P et al. conducted a study in an HIV-infected cohort study; 100 HIV-infected, antituberculosis therapy (ATT)-naive patients, with a mean age of 40 years, diagnosed with tuberculosis (TB) were enrolled. Disseminated TB was present in 58 patients, while the rest had pleuropulmonary TB. At baseline, 40% had liver function test (LFT) abnormalities, but there was no significant difference in baseline characteristics between those with abnormal and normal LFTs, including age, body mass index (BMI), albumin, or CD4 cell count. Most patients (61) were already on antiretroviral therapy (ART), and 73 were on cotrimoxazole. ART regimens included nonnucleoside reverse transcriptase inhibitors (efavirenz or nevirapine) and protease inhibitors (lopinavir or atazanavir). During the study, 99 patients developed transaminitis, with 85 having mild elevations. At 8 weeks, 32 patients were started on ART, and 12 of those already on ART had significant LFT derangements. Hyperbilirubinemia was found in 48 patients, but only 9 had significant elevations. Patients with baseline LFT abnormalities were more likely to develop new significant LFT abnormalities during follow-up. By the study's end, 14 patients had significant transaminitis, and 11 had a mixed pattern of liver injury. No patient developed acute liver failure, and there were no mortalities. (12)

INH is most commonly implicated in hepatotoxicity, while ethambutol and streptomycin are generally not considered hepatotoxic. INH hepatotoxicity is largely attributed to the formation of reactive metabolites during its metabolism in the liver. The enzyme N-acetyltransferase 2 (NAT2) plays a significant role in metabolizing INH to acetyl hydrazine, which is further metabolized by cytochrome P4502E1 (CYP2E1) into toxic metabolites. Slow acetylators, due to genetic variations in NAT2, are at higher risk for accumulating these toxic intermediates, leading to hepatocellular damage. In addition to slow acetylation, the presence of CYP2E1 variants further increases the risk of hepatotoxicity in patients on INH. Rifampicin, though less frequently hepatotoxic when

used alone, enhances the hepatotoxic effects of INH by inducing enzymes involved in the metabolism of INH, leading to increased production of toxic metabolites. Rifampicin itself undergoes hepatic metabolism to desacetyl rifampicin, a non-toxic metabolite. However, rifampicin's induction of cytochrome P450 enzymes, particularly CYP3A4, plays a pivotal role in amplifying INH-induced hepatotoxicity. Pyrazinamide is also known to be hepatotoxic, with its toxicity being dose-dependent. Its metabolism leads to the production of pyrazinoic acid, and prolonged use or use in higher doses increases the likelihood of liver injury.

A study by Yee D et al on 430 patients treated for active TB between 1990 and 1999 assessed the incidence and risk factors of major side effects from first-line anti-TB drugs, including pyrazinamide, isoniazid, rifampin, and ethambutol. Adverse effects leading to therapy modification, discontinuation, or hospitalization were analysed. The overall incidence of major adverse effects was highest with pyrazinamide at 1.48 per 100 person-months (95% CI, 1.31–1.61), followed by isoniazid (0.49), rifampin (0.43), and ethambutol (0.07). Key risk factors for adverse events included female sex (adjusted hazard ratio [aHR], 2.5), age over 60 years (aHR, 2.9), birthplace in Asia (aHR, 2.5), and HIV-positive status (aHR, 3.8). Specifically, pyrazinamide-related side effects were associated with older age (aHR, 2.6) and Asian birthplace (aHR, 3.4), while rifampin-related events were linked to older age (aHR, 3.9) and HIV status (aHR, 8.0). Pyrazinamide-induced hepatotoxicity and rash occurred more frequently than with other first-line drugs, underscoring its elevated risk profile. (13)

Mahmood K et al conducted a study in Pakistan which showed an incidence rate of 19.76% of anti-tubercular therapy (ATT)-induced hepatotoxicity. Female patients were more affected by hepatotoxicity compared to males (26.3% vs. 19.7%). A significant finding was that 91% of the patients who developed hepatotoxicity had a body mass index

(BMI) less than 18.5 kg/m² ($p < 0.01$), indicating that the majority of affected individuals were underweight. Additionally, most of these patients were anaemic and had low serum albumin levels, suggestive of a lean body mass and poor nutritional status, factors that may have contributed to their vulnerability to hepatotoxicity. The severity of hepatotoxicity was greater among patients who were AFB smear-positive, highlighting a potential correlation between bacterial load and liver injury. Several predisposing factors for hepatotoxicity were identified, including the concomitant use of alcohol, paracetamol, and low serum cholesterol levels. These factors appeared to exacerbate the risk of liver injury during ATT. Among the anti-tubercular drugs, isoniazid was identified as the primary agent responsible for hepatotoxicity in 37 patients (55.21%, $p < 0.01$), followed by rifampicin in 23 patients (34.21%) and pyrazinamide in 7 patients (10.5%). The majority of hepatotoxicity cases (61%) occurred within two weeks of initiating ATT, and the liver injury typically manifested as mild to moderate elevations in alanine transaminase (ALT) and aspartate transaminase (AST) levels. (6)

Ramappa V et al described several host-related factors that increase the risk of anti-TB DILI. Age is a well-known risk factor, with older patients, particularly those above 50, being at higher risk due to reduced liver function and decreased drug clearance. Studies have also shown a higher incidence of DILI in females, attributed to differences in drug metabolism enzymes such as CYP3A4. Nutritional status also plays a critical role, as malnutrition, which is common in TB patients, impairs liver function and detoxification pathways, increasing susceptibility to liver injury. Alcohol intake further exacerbates the risk, as it induces hepatic enzymes, thereby increasing the production of reactive metabolites. Concomitant infections, particularly chronic viral hepatitis (hepatitis B and C) and HIV, significantly heighten the risk of hepatotoxicity. Co-infected individuals have a higher rate of liver injury due to overlapping mechanisms of liver damage and the

potential for drug-drug interactions in cases of concurrent antiretroviral therapy (ART). Genetic variations significantly influence individual susceptibility to anti-TB DILI. Polymorphisms in genes coding for metabolizing enzymes like NAT2 and CYP2E1 are associated with higher rates of DILI. (14)

Hussain Z et al described genetic polymorphisms causing AT-DILI. N-acetyltransferase 2 (NAT2) and glutathione-S-transferase (GST) genes are major susceptibility factors for antitubercular therapy (ATT)-induced hepatitis. The NAT2 enzyme, which is involved in metabolizing carcinogenic arylamines and various drugs, exhibits genetic variation leading to either slow or rapid acetylation phenotypes. Slow acetylators are at a higher risk of developing severe hepatotoxicity compared to rapid acetylators. Similarly, deficiencies in GST activity due to homozygous null mutations at GSTM1 and GSTT1 loci can increase susceptibility to drug-induced liver injury. Polymorphisms at these loci have also been associated with various forms of liver damage, including hepatocellular carcinoma. (15)

To establish causality, Das S et al discussed using various causality assessment scales to evaluate drug-induced liver injury (DILI) cases. The aim was to determine the agreement between two non-specific scales (WHO and Naranjo) and three liver-specific scales (RUCAM, M & V, and DDW–J) in assessing 33 DILI cases. Results showed that good agreement was only observed between the RUCAM and DDW–J scales, likely due to the similarity in their causality criteria. However, the study found poor agreement between other scales, including Naranjo and RUCAM, Naranjo and WHO–UMC, and M & V and RUCAM, highlighting discrepancies due to subjective assessments and different causality criteria.(16)In most of the studies cited, RUCAM is used to assess causality.

Saha A et al conducted a study in 2016, that reviewed 787 patient charts, of which 253 were included for analysis. Of these, 24 patients (9.48%) developed drug-induced liver injury (DILI). The patients were treated under different regimens: 193 received Category 1 treatment, 60 received Category 2 treatment, 81 received fixed-dose treatment, and 172 had doses based on body weight. Out of these, 42 patients were on intermittent regimens, while 211 received daily treatment. Risk factors such as chronic alcohol consumption (26 patients), hepatitis B infection (2 patients), hepatitis C infection (1 patient), HIV infection (37 patients), and chronic TB (21 patients) were present in the population. However, none of these risk factors had a statistically significant association with the occurrence of DILI. The odds ratios for factors like chronic alcohol consumption (OR: 2.59 unadjusted, 1.47 adjusted), hepatitis B (OR: 9.87 unadjusted), and HIV (OR: 1.61 unadjusted, 0.60 adjusted) did not show a strong correlation with DILI. Similarly, other variables such as age, sex, weight, body mass index, dosing regimen, and treatment category also had poor correlations with DILI, suggesting that these factors were not significant predictors of liver injury in this cohort. This study signifies that the so-called known predictive factors for DILI may not be as significant as previously thought. (3)

In a prospective study conducted by Agal S et al at the Department of Internal Medicine and Gastroenterology, Jagjivanram Hospital, and the Department of Gastroenterology, Bombay Hospital, Mumbai, India, patients diagnosed with tuberculosis and undergoing antitubercular therapy (ATT) were monitored for hepatotoxicity. The study divided patients into three groups: Group A (n = 21), those who developed hepatotoxicity during periodic monitoring; Group B (n = 24), those who presented with ATT-induced hepatotoxicity; and Group C (n = 179), those who did not develop hepatotoxicity. In Group A, 66.6% (14 patients) were diagnosed during the asymptomatic phase, while seven patients exhibited symptomatic hepatitis, but none developed icteric illness. No

mortality occurred in Group A. However, in Group B, all patients exhibited symptomatic hepatitis, with 75% presenting with icteric hepatitis, and there was a mortality rate of 16.6% (four patients). Of the 41 surviving patients from Groups A and B, reintroduction of ATT was successful in 97.4% (38/39) after normalization of liver function. Reintroduction was not attempted in two Group B patients due to decompensated liver disease.(17)

Sunil Kumar N et al conducted a study on 133 cases of all cause drug-induced liver injury (DILI) over four years, 69 patients were men and 64 were women. Based on the R factor, 61.6% of patients were classified as hepatocellular, 22.5% as mixed, and 15.7% as cholestatic types of DILI. The mean age varied slightly across groups, with hepatocellular patients averaging 44.5 years, mixed injury patients 45.6 years, and cholestatic injury patients 51.1 years. Symptoms such as anorexia, jaundice, vomiting, pruritus, and abdominal pain were common, with pruritus being more prevalent in cholestatic injury cases. Drug exposure duration was the longest in the mixed injury group. ATT drugs were the most frequent cause of DILI (37.5%), followed by neuropsychiatric drugs, antibiotics, and complementary and alternative medicines (CAMs). Persistent DILI occurred in 13 patients, mostly attributed to ATT drugs and CAMs. Mortality was recorded in 18 patients, with a rate of 13.5%, and ATT drugs were implicated in over half of the deaths. Non-survivors were generally older and had higher MELD scores, serum creatinine, INR, and bilirubin levels. Predictors of mortality included ascites, prolonged drug exposure, higher MELD scores, and elevated creatinine, INR, and bilirubin levels. Comparison between ATT-induced DILI and non-ATT DILI cases revealed more vomiting, longer drug exposure, and poorer clinical outcomes in the ATT group, though recovery rates were higher in non-ATT cases.(18)

A study by Rathi C et al included 82 individuals diagnosed with drug-induced liver injury (DILI) between 2014 and 2015 (41 men; median age 38 years) and identified antitubercular therapy (ATT) as the most commonly implicated drug, responsible for 49% of cases. Other drugs associated with DILI included antiepileptic drugs (12%), complementary and alternative medicine (CAM) (10%), antiretroviral drugs (9%), and non-steroidal anti-inflammatory drugs (6%). Out of 13 deaths, 8 were liver-related, with significantly higher liver-related mortality observed in patients with ATT-induced DILI (17.5%) compared to those without (2.4%) ($P = 0.02$). There was no significant difference in mortality across different types of liver injury (hepatocellular, cholestatic, or mixed patterns). Laboratory parameters measured one week after drug discontinuation provided better predictions of mortality than those at the time of DILI recognition. Multivariate logistic regression analysis identified jaundice, encephalopathy, the Model for End-Stage Liver Disease (MELD) score, and alkaline phosphatase levels at one week as independent predictors of mortality.(19)

The American Thoracic Society (ATS) guidelines on ATT-induced drug-induced liver injury (DILI) highlight several risk factors that increase the likelihood of developing this condition, including chronic ethanol consumption, viral hepatitis, pre-existing liver disease, pregnancy or the postpartum period, concomitant use of hepatotoxic medications, baseline abnormal liver function tests, coexisting HIV infection, and age over 35 years. A study by Latief M et al on 190 patients with tuberculosis on ATT found that DILI occurred in 8.4% of cases, with early DILI (within 2 weeks) affecting 62.5% and late DILI (after 2 weeks) affecting 37.5%. Among those with early DILI, 60% were symptomatic, while 66.6% of those with late DILI were symptomatic. Notably, one patient with early DILI developed acute liver failure and died despite supportive measures. The study revealed significant gender differences in DILI incidence, with a

higher prevalence among females, and identified extrapulmonary tuberculosis as a significant predictor of DILI. Age and BMI did not show a significant impact on DILI development. The study suggests biweekly liver function tests during the intensive phase of ATT and every two months thereafter, particularly for high-risk individuals. Management according to ATS guidelines involves restarting Rifampin once ALT levels drop below twice the upper limit of normal (ULN), with or without Ethambutol, and reintroducing Isoniazid after 3–7 days while monitoring ALT levels. If symptoms recur or ALT increases, the last drug added should be stopped. In cases of severe or prolonged hepatotoxicity, Pyrazinamide may be permanently discontinued, though it can be reintroduced in milder cases. (20)

Raj Mani SS et al conducted a study from April 2013 to May 2014, included a total of 393 tuberculosis patients, with the baseline characteristics of those on daily and DOTS regimens well matched in terms of age and gender. The DOTS arm, however, had lower rates of HIV infection and disseminated disease but higher rates of undernutrition compared to the daily regimen group. Of the 388 patients who developed ATT DILI, 38 were included for incidence calculation, yielding an incidence rate of 9.7% overall. The incidence was notably lower in patients on the DOTS regimen (3.5%) compared to the daily regimen (14%). Among the 43 patients who developed DILI, 53% were male, and 56% had disseminated disease. The majority (90.7%) were on a weight-based daily regimen. Common symptoms included vomiting (58%) and jaundice (30.2%), though 16.3% of patients were asymptomatic and diagnosed solely through elevated liver enzymes. Clinical signs of icterus were observed in 65% of cases, while severe liver failure was rare but present in 9.3% of patients. Liver function tests (LFTs) revealed that 60% of patients had elevated liver enzymes with bilirubin, followed by a cholestatic pattern in 26% and isolated enzyme elevation in 14%. WHO standards classified 35% of

the cases as severe hepatitis, with chronic liver disease identified as a significant risk factor for its development. Most cases of DILI (76.7%) occurred within the first two months of treatment, highlighting the importance of careful monitoring during this period for patients with clinical risk factors. Significant risk factors for DILI identified through multivariate logistic regression included HIV infection, a daily regimen, disseminated disease, hypoalbuminemia, and chronic liver disease. However, factors like older age, chronic hepatitis B or C infection, or a history of jaundice were not significant predictors. A large proportion (90.7%) of patients required hospitalization, and 9.3% required intensive care, with a mortality rate of 4.7%. Alternative drug regimens were initiated in 69.8% of patients, with successful reintroduction of hepatotoxic drugs in several cases. Pyrazinamide rechallenge was successful in all six cases where it was attempted, though seven patients developed rechallenge hepatitis. (21)

Singla R et al observed 237 consecutive patients who developed drug-induced hepatotoxicity (DIH) while on anti-tuberculosis (anti-TB) treatment. Four of these patients died, three from acute liver failure and one from progressive pulmonary tuberculosis leading to acute respiratory failure. Fifty-eight patients were excluded for various reasons, including chronic alcoholism, concurrent use of hepatotoxic drugs, HIV seropositivity, and recent acute viral hepatitis. This left 175 patients for the final analysis. Among the DIH cases, 25.7% had pulmonary TB, 55.4% had extrapulmonary TB, and 18.9% had miliary or disseminated TB. A significantly higher proportion of DIH cases presented with extrapulmonary TB compared to controls ($P<0.01$). Additionally, DIH cases with pulmonary TB showed more severe disease on chest radiographs compared to controls, with 82.2% of DIH cases exhibiting moderate to far advanced disease, in contrast to 54.7% of controls ($P<0.01$). The majority of DIH cases presented with symptoms such as nausea (90.2%), vomiting (65.7%), abdominal pain (28%), and

jaundice (43.4%), while 6.9% were asymptomatic and diagnosed based solely on elevated liver enzymes. Baseline laboratory tests revealed that DIH cases had significantly lower serum total protein and albumin levels compared to controls. Hypoalbuminemia (serum albumin <3.5 g/dl) was a key factor associated with the development of DIH. Univariate analysis identified several risk factors for DIH, including age over 35 years, TB site, disease severity on chest radiographs, low mid-arm circumference (MAC), and low baseline serum proteins. Multivariate analysis confirmed that age over 35, MAC less than 20 cm, and hypoalbuminemia were significant independent predictors of DIH. Regarding treatment, only 14.3% of DIH patients received DOTS (thrice-weekly intermittent treatment), while the majority (85.7%) were on a daily anti-TB regimen. The median time to the onset of DIH was 23 days, with liver function normalizing after a median of 18 days. (22)

Managing DILI in tuberculosis (TB) patients is complex, as it necessitates a balance between treating the infection and minimizing the risk of severe liver damage. A study by Moosa MS et al involving 79 participants rechallenged with ATT after developing DILI found that 18% experienced a positive rechallenge, meaning they had a recurrence of liver injury after reintroduction of ATT. Positive rechallenge was associated with female sex (P = 0.039) and being treated for a first episode of tuberculosis (P = 0.032). Pyrazinamide was the most frequent offender, with a significantly higher rate of positive rechallenge (9 out of 46 cases) compared to rifampicin (2 out of 78) and isoniazid (2 out of 74) (P = 0.005). One case of pyrazinamide rechallenge resulted in a fatal hypersensitivity reaction, underscoring the drug's high hepatotoxic potential. The median time from ATT interruption to rechallenge was similar between patients with positive and negative outcomes—12 days versus 13 days, respectively (P = 0.719). Among HIV-positive participants, the majority (79%) had their antiretroviral therapy (ART) interrupted at the

time of liver injury. Most of these patients successfully resumed ART within eight weeks of rechallenge, with 21 of 26 returning to their previous ART regimen. (23)

Soni H et al conducted a study describing the reintroduction of ATT after DILI. It is typically performed using one of three regimens: sequential, incremental, or concomitant. A systematic review and network meta-analysis of four randomised studies involving 577 patients compared the effectiveness of these regimens in reducing recurrence rates. Of these, 243 patients were treated with sequential regimens, 241 with incremental regimens, and 93 with concomitant regimens. The analysis revealed that incremental reintroduction had the highest probability of reducing the recurrence of ATT-related hepatitis, with an odds ratio (OR) of 0.33 compared to sequential reintroduction and 0.24 compared to concomitant reintroduction. Although none of these findings were statistically significant, the rank probability analysis suggested that incremental regimens had a 0.68 probability of being the best option, followed by sequential regimens at 0.30. Concomitant reintroduction had the lowest probability of success, with only a 0.02 chance of being the best option. Despite these findings, a pairwise meta-analysis indicated no statistically significant differences between the reintroduction regimens (OR 1.08; 95% CI 0.53–2.19). The studies also highlighted the high risk of bias due to missing data and flaws in randomization methods, emphasizing the need for larger, well-designed trials to confirm these results. (24)

In a prospective study from India by Sharma SK et al, 237 patients with DILI from ATT were analysed. The study found that 16% of patients had serological evidence of acute viral hepatitis, primarily hepatitis A and E, indicating the need to differentiate DILI from viral causes in settings with high hepatitis prevalence. Notably, 55.4% of patients had extrapulmonary TB, and 14.3% were undergoing directly observed treatment. The latency period for liver function stabilization in these patients was 23 days, and the median

normalization time was 18 days. The recurrence rate of DILI was 10.9%, with no significant difference across the three treatment arms in the study. Pre-treatment serum albumin levels were the only significant predictor of recurrence, with lower levels associated with a higher likelihood of recurrence. This highlights the importance of nutritional status in determining the risk of DILI. (25)

Costiniuk CT et al conducted a study in a high-prevalence HIV cohort that analysed 53 patients with TB-DILI, 42 of whom were rechallenged with ATT. The majority of rechallenged patients (88%) did not experience recurrence, while 12% had recurrent episodes. Younger age and higher bilirubin levels were associated with a higher risk of recurrence, while comorbidities such as hepatitis B or C and alcohol abuse did not significantly affect outcomes. (26)

To compare the effectiveness of two commonly used reintroduction regimens, Chaitra K et al enrolled 50 patients with ATT-induced DILI and randomized to either the ATS or BTS regimen. The ATS regimen resulted in better outcomes, with no deaths and a lower recurrence rate compared to the BTS regimen. Specifically, the ATS regimen led to a higher success rate in reintroducing hepatotoxic drugs, particularly in cases of hepatocellular DILI. In contrast, patients with cholestatic DILI had poorer outcomes, with eight deaths occurring in this group. Overall, the study found that the ATS regimen significantly outperformed both the BTS and all-drug reintroduction regimens, making it the preferred approach for managing ATT-DILI. (27)

Malnutrition emerged as a critical factor in the recurrence of DILI in several studies. Lower BMI and serum albumin levels were consistently identified as predictors of recurrence, with strong predictive values (AUC of 0.953 for BMI and 0.988 for albumin). These findings underscore the importance of addressing nutritional deficiencies before

and during ATT to reduce the risk of DILI recurrence. Zuberi FF et all concluded that both the ATS and BTS regimens showed similar recurrence rates (9.8% and 11.1%, respectively), suggesting that the choice of regimen may not be as important as ensuring adequate nutritional support and close monitoring of liver function during treatment. (28)

Due to the lack of reliable pre-treatment risk stratification methods for DILI, some experts recommend routine liver function monitoring in all patients undergoing ATT, particularly within the first two weeks of treatment, when DILI is most likely to occur. Early detection of subclinical DILI could allow for prompt drug withdrawal and prevent progression to severe liver damage, including acute liver failure. Routine monitoring also enables faster normalisation of liver enzymes, potentially reducing treatment interruptions and improving overall outcomes.

Table 1: The studies included in the literature review are presented in a tabular format on the next page.

Sr. No.	Title	Authors	Year	Design	Summary
1.	Hepatotoxicity with anti-TB drugs: the risk factors	Mahmood K et al	2006	Prospective cohort study	Among 339 patients receiving antitubercular therapy (ATT), 67 (19.76%) developed hepatotoxicity, with a higher incidence in females (26.3%) compared to males (19.7%). Factors like low BMI, anaemia, and low albumin levels were significant predictors. Isoniazid was the leading cause (55.21%), followed by Rifampicin (34.21%) and Pyrazinamide (10.5%).
2.	Toxic Hepatitis with Isoniazid and Rifampin: A Meta-analysis	Steele MA et al	1991	Meta-analysis	Pooled data from 6,105 patients on Isoniazid (INH) + Rifampin (RMP) revealed a 2.55% incidence of toxic hepatitis, significantly higher than the 1.6% in 2,053 patients on INH without RMP ($p = 0.048$). The risk of hepatitis was also higher in the INH+RMP group compared to RMP-only regimens (1.1%, $p = 0.008$).
3.	Drug-induced liver injury: a	Hosack T et al	2023	Review article	Classified drug-induced liver injury (DILI) into intrinsic and idiosyncratic types.

	comprehensive review				Intrinsic DILI is dose-dependent, predictable, and rapid, often caused by drugs like paracetamol. Idiosyncratic DILI is unpredictable, varying in onset and severity, with immune and non-immune subtypes. Severity is graded using the CTCAE framework.
4.	Guideline review: EASL clinical practice guidelines: drug-induced liver injury (DILI)	Brennan PN et al	2021	Review article	DILI can be classified into phenotypes based on liver enzyme derangements, such as hepatocellular (R>5), cholestatic (R≤2), and mixed (R between 2-5). Chronic forms persist beyond one year. Common drugs involved include antimicrobials, anticonvulsants, and antineoplastics. Additional phenotypes include drug reaction with eosinophilia, autoimmune hepatitis, and liver tumours.
5.	Drug-induced liver injury from antituberculosis treatment: a retrospective study from a	Abbara A et al	2017	Retrospective case-control study	Of 1529 TB patients, 6.9% developed DILI, with alcohol consumption, high doses of isoniazid/pyrazinamide, and low body weight identified as risk factors. Most cases resolved without stopping ATT. Mortality due to DILI was 4.8%, particularly in vulnerable populations, such as those co-infected with HIV.

	large TB centre in the UK				
6.	Risk Factors of Hepatotoxicity During Anti-Tuberculosis Treatment	Anand A et al	2006	Prospective cohort study	The study observed a higher incidence of liver dysfunction in TB patients with chronic HBV on ATT (37.5%) compared to controls without HBV (10.2%) and HBV carriers not on ATT (12.8%). Older age, HBsAg positivity, and underlying liver disease significantly increased the risk of hepatotoxicity. Among 69 patients with ATT-induced hepatitis, 17 developed serious complications, including hepatic encephalopathy, fulminant hepatic failure, and subacute hepatic failure. 7 patients died, with most fatalities occurring in those not promptly discontinuing ATT.
7.	Antitubercular therapy induced liver function tests abnormalities in HIV	Puri P et al	2017	Prospective cohort study	In a study of 100 HIV patients, 99 developed liver function test (LFT) derangements after starting anti-tuberculosis treatment (ATT). Significant transaminase elevations were more frequent in those on both antiretroviral therapy (ART) and ATT and in patients

	infected individuals				with pre-existing LFT abnormalities. Despite this, only 15 required liver-sparing ATT, and no cases of acute liver failure or mortality occurred. Baseline LFT abnormalities were similar between ART and non-ART groups.
8.	Incidence of Serious Side Effects from First-Line ATT among Patients Treated for Active Tuberculosis	Yee D et al	2003	Retrospective cohort study	430 patients treated for active TB between 1990 and 1999 were enrolled. The highest incidence of adverse effects occurred with pyrazinamide (1.48 per 100 person-months), followed by isoniazid, rifampin, and ethambutol. Risk factors for major side effects included female sex, age over 60, Asian birthplace, and HIV-positive status. Pyrazinamide- and rifampin-associated adverse effects were especially linked to older age and HIV infection, highlighting a higher-than-expected risk of pyrazinamide-induced hepatotoxicity.
9.	Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms	Ramappa V et al	2013	Review article	Key factors that increase the risk of DILI include age, especially among patients over 50. Females also show a higher incidence of DILI. Malnutrition and alcohol intake increase the risk of DILI. Chronic viral infections also increase

	and Management				DILI risk. Genetic polymorphisms in metabolising enzymes like NAT2 and CYP2E1 also influence susceptibility to DILI.
10.	A nomogram model to predict the risk of drug-induced liver injury in patients receiving anti-tuberculosis treatment	Ji S et al	2023	Retrospective cohort study	This study enrolled 1,979 patients and identified an incidence of DILI of 4.2% (n = 83). Patients were divided into training (n = 1,121) and two validation groups (n = 492 and n = 264). Five independent factors were included in the final nomogram model for DILI prediction: age, total bilirubin, uric acid, neutrophil count, and alcohol consumption. The model's AUCs were 0.833, 0.668, and 0.753 for the training and validation groups, respectively, with strong calibration and decision curve analysis (DCA) results.
11.	Predicting drug-induced liver injury from anti-tuberculous medications by early	Patterson B et al	2020	Retrospective cohort study	In a study of 1,247 tuberculosis (TB) patients treated across five sites in Northwest London (2015–2018), 103 cases (8.3%) of ATT-associated DILI were identified. Notably, 60 cases (58.3%) developed after two weeks of treatment. The risk of late TB-DILI increased 2.2-fold for every 30 U/L increase in baseline ALT

	monitoring of liver tests				(OR 2.16) and 2.1-fold for every 30 U/L rise in ALT at two weeks (OR 2.06).
12.	Antituberculosis drug-induced hepatitis: risk factors, prevention and management	Hussain Z et al	2003	Review article	Isoniazid combined with rifampicin accelerates liver toxicity due to a synergistic effect. Genetic factors such as polymorphisms in N-acetyltransferase 2 (NAT2) and glutathione-S-transferase (GST) increase susceptibility to hepatotoxicity. Slow acetylators of NAT2, along with deficiencies in GST activity, make individuals more prone to drug-induced liver injury.
13.	Agreement Among Different Scales for Causality Assessment in Drug-Induced Liver Injury	Das S et al	2018	Comparative assessment study	The researchers compared two non-specific scales, the WHO–UMC and Naranjo, with three liver-specific scales, the RUCAM, Maria & Victorino (M & V), and DDW–J. Among the 33 cases of DILI assessed, good agreement was found between the RUCAM and DDW–J scales, likely due to their similar causality criteria.

14.	Prevalence of Hepatotoxicity from ATT	Saha A et al	2016	Retrospective cohort study	Data from 253 patients undergoing antituberculosis therapy were analysed. Among these, 24 patients (9.48%) developed DILI. The treatment regimens varied, with patients receiving Category 1, Category 2, fixed-dose, or body weight-based treatments. Risk factors such as chronic alcoholism (26 patients), hepatitis B (2 patients), hepatitis C (1 patient), HIV (37 patients), and chronic TB (21 patients) were identified, but none showed a statistically significant association with DILI. The OR for these factors, as well as other variables like age, sex, and treatment regimen, indicated that known predictors for DILI may not be as significant as previously thought.
15.	Monitoring and management of ATT induced hepatotoxicity	Agal S et al	2005	Prospective cohort study	Patients who developed hepatotoxicity were categorised into Group A (21 patients), while those who did not were placed in Group C (179 patients). Additionally, patients presenting directly with ATT-induced hepatotoxicity were categorised as Group B (24 patients) for comparison.

					Results: In Group A, 66.6% (14 patients) were diagnosed during the asymptomatic period, while 7 patients had symptomatic hepatitis, with none experiencing icteric illness. No deaths occurred in this group. In contrast, all patients in Group B had symptomatic hepatitis, with 75% experiencing icteric hepatitis, and there was a mortality rate of 16.6% (4 patients). Among the 41 patients from Groups A and B who survived, reintroduction of ATT after normalization of liver functions was successful in 38 out of 39 patients (97.4%). Reintroduction was not attempted in 2 patients from Group B due to decompensated liver disease.
16.	Outcomes and Predictors of Mortality in	Kumar S et al	2020	Prospective cohort study	In a study of 133 cases of drug-induced liver injury (DILI) over four years, 61.6% were classified as hepatocellular, 22.5% as mixed, and 15.7% as cholestatic. The mean

	Patients with Drug-Induced Liver Injury at a Tertiary Hospital in South India: A Single-Centre Experience				ages were 44.5 years for hepatocellular, 45.6 years for mixed, and 51.1 years for cholestatic injury. Antituberculosis therapy (ATT) drugs were the most common cause of DILI (37.5%). The study recorded a mortality rate of 13.5%, with non-survivors generally being older and having higher MELD scores. Predictors of mortality included ascites, prolonged drug exposure, and elevated creatinine, INR, and bilirubin levels, with poorer outcomes associated with ATT-induced DILI.
17.	Drug-Induced Liver Injury at a Tertiary Hospital in India: Aetiology, Clinical Features and Predictors of Mortality	Rathi C et al	2017	Prospective cohort study	A study of 82 patients with drug-induced liver injury (DILI) from 2014-2015 found that antitubercular therapy (ATT) was the most common cause (49%) and had significantly higher liver-related mortality (17.5%) compared to other drugs (2.4%). Mortality predictors included jaundice, encephalopathy, MELD score, and alkaline phosphatase levels one week after discontinuing the drug. Overall, 8 out of 13 deaths were liver-related, and laboratory parameters post-drug cessation were more

					reliable for predicting outcomes than initial recognition.
18.	Novel risk factors and early detection of anti-tubercular treatment induced liver injury-Looking beyond American Thoracic Society Guidelines	Latief et al	2017	Prospective cohort study	8.4% of TB patients on ATT developed DILI, with early DILI affecting 62.5%. More females experienced DILI, and extrapulmonary TB was a significant predictor. Biweekly liver function tests are recommended during the intensive phase of ATT for high-risk individuals, and the reintroduction of drugs should follow ALT monitoring according to ATS management guidelines.
19.	Predicting antitubercular drug-induced liver injury and its outcome and introducing a	Raj Mani SS et al	2021	Prospective cohort study	A study on 393 tuberculosis patients found an overall ATT-induced DILI incidence rate of 9.7%, with lower incidence in the DOTS regimen (3.5%) compared to the daily regimen (14%). Risk factors for DILI included HIV infection, daily regimens, disseminated disease, hypoalbuminemia,

	novel scoring system				and chronic liver disease. Most DILI cases (76.7%) occurred within the first two months. Severe hepatitis developed in 35% of cases, and 4.7% mortality was reported. Successful reintroduction of hepatotoxic drugs was achieved, with Pyrazinamide rechallenge succeeding in all cases attempted.
20.	Evaluation of risk factors for ATT induced hepatotoxicity	Singla R et al	2010	Case-control study	The study found that in the DILI subgroup, 55.4% had extrapulmonary TB, and 82.2% of pulmonary TB cases had moderate to severe disease. Common symptoms included nausea (90.2%) and jaundice (43.4%). Risk factors for DIH were age over 35, low mid-arm circumference (MAC), and hypoalbuminemia. Most DIH cases were on a daily anti-TB regimen (85.7%), with a median onset of DIH at 23 days and liver function normalizing after 18 days.
21.	Rechallenge after anti-tuberculosis drug-induced liver injury in	Moosa MS et al	2022	Randomised controlled trial	A study involving 79 patients who were rechallenged with anti-tuberculosis therapy (ATT) after DILI showed an 18% positive rechallenge rate, with female sex and first-episode TB as significant risk factors.

	a high HIV prevalence cohort				Pyrazinamide was the primary drug linked to positive rechallenge, with a notable incidence compared to rifampicin and isoniazid. One case resulted in a fatal hypersensitivity reaction. Most HIV-positive participants managed to resume their antiretroviral therapy within eight weeks after rechallenging.
22.	Risk of hepatitis with various reintroductio n regimens of anti-tubercular therapy: a systematic review and network meta-analysis	Soni H et al	2020	Systematic review and network meta-analysis	A study on reintroducing anti-tuberculosis therapy (ATT) after drug-induced liver injury (DILI), compared three regimens: sequential, incremental, and concomitant. A systematic review of four randomized studies involving 577 patients found that incremental reintroduction had the highest likelihood of reducing recurrence rates, with an odds ratio (OR) of 0.33 compared to sequential and 0.24 to concomitant regimens. Despite a rank probability analysis favouring incremental regimens, no statistically significant differences were observed in a pairwise meta-analysis (OR 1.08; 95% CI 0.53–2.19).

23.	Tuberculous Drug-induced Liver Injury and Treatment Re-challenge in HIV Co-infection	Costiniuk CT et al	2015	Retrospective cohort study	A study was done on 53 HIV-positive patients with tuberculosis drug-induced liver injury (TB-DILI), focusing on 42 who were rechallenged with anti-tuberculosis therapy (ATT). The findings revealed that 88% of rechallenged patients did not experience a recurrence of liver injury, while 12% did. Factors such as younger age and elevated bilirubin levels were linked to a higher risk of recurrence. However, comorbidities like hepatitis B or C and alcohol abuse did not significantly impact the outcomes.
24.	ATT induced liver injury: clinical profile and outcome of various reintroduction regimen	Chaitra K et al.	2022	Randomized controlled trial	50 patients were enrolled to compare the ATS and BTS regimens for reintroducing anti-tuberculosis therapy after drug-induced liver injury. The ATS regimen showed better outcomes, with no deaths and a lower recurrence rate, particularly in hepatocellular DILI cases.
25.	Comparison of British Thoracic Society and	Zuberi FF et al.	2013	Randomized controlled trial	Similar DILI recurrence rates for ATS and BTS regimens. Malnutrition being a significant factor in the recurrence of DILI.

	American Thoracic Society reintroduction guidelines for ATT induced liver injury				Lower BMI and serum albumin levels are strong predictors of recurrence.
26.	Effect of chronic kidney disease on adverse drug reactions to anti-tubercular treatment: a retrospective cohort study (29)	Datta D et al	2024	Retrospective cohort study	In a cohort of 1,815 patients on antitubercular therapy (ATT), 4.1% (75 patients) had chronic kidney disease (CKD). CKD patients experienced significantly higher rates of adverse drug reactions (ADRs) at 48%, compared to 13.7% in those with normal kidney function. Additionally, 32.6% of CKD patients developed severe ADRs, versus 15.1% in non-CKD patients. Common ADRs in CKD included hepatobiliary, neuropsychiatric, renal, and gastrointestinal issues. CKD was identified as an independent predictor of ADRs, increasing the likelihood of their occurrence (OR: 4.96, 95% CI: 2.79–8.82).

27.	Incidence and Risk Factors of Serious Adverse Events during ATT in Rwanda: A Prospective Cohort Study (30)	Lorent N et al	2011	Prospective cohort study	253 TB patients were studied, with 66% being HIV-positive and having a median CD4 count of 104 cells/mm³. Serious adverse events (AEs) occurred in 26% of the cohort, more frequently in HIV-positive patients (35%) compared to HIV-negative ones (7%). Common AEs included concurrent infections, drug-induced hepatitis, and paradoxical reactions. HIV infection and extrapulmonary TB were independent risk factors for AEs. AEs doubled the risk of unsuccessful treatment outcomes and significantly increased the risk of death. Fifty-five patients died, with 48 being HIV-positive, many deteriorating gradually before death.
28.	Anti-tuberculosis drug induced hepatitis – a Sri Lankan experience (31)	WV Senaratne et al	2006	Prospective observational study	A study of 783 TB patients, aged 11 to 84 years (mean 45.2), found that 9.5% developed anti-tuberculosis drug-induced hepatotoxicity (AIH), primarily within the first two weeks of treatment. Most participants were male (72.2%) and pulmonary TB-positive (92.1%). Significant AIH risk factors included age over 60, low body weight, and rifampicin

					overdose. AIH management involved adjusting regimens and reintroducing standard treatment once liver enzymes normalized, though some patients required alternative regimens. Despite these interventions, a few deaths occurred. Age, low weight, and rifampicin overdose were identified as the strongest AIH predictors.
29.	Evaluation of prognostic significance of haematological profiles after the intensive phase treatment in pulmonary tuberculosis patients from Romania (32)	Ştefanescu S et al	2021	Prospective observational study	This study involved 106 new PTB patients, of which 90 were selected after exclusion criteria. Among them, 63 had negative culture conversion after two months of anti-TB treatment. The study assessed various haematological parameters before and after two months of treatment. The analysis revealed that most haematological values significantly decreased after treatment in culture-negative patients. The study concluded that certain parameters, particularly NLR, PLR, and SII, were associated with culture conversion but were not strong single predictors. However, combined predictive models demonstrated better diagnostic value for culture outcomes.

30.	Safety of 3 Different Reintroduction Regimens of Antituberculosis Drugs after Development of Antituberculosis Treatment–Induced Hepatotoxicity	Sharma SK et al	2010	Prospective observational study	237 patients with DILI from ATT were analysed. The study found that 16% of patients had serological evidence of acute viral hepatitis, primarily hepatitis A and E. Notably, 55.4% of patients had extrapulmonary TB, and 14.3% were undergoing directly observed treatment. The latency period for liver function stabilization in these patients was 23 days, and the median normalization time was 18 days. The recurrence rate of DILI was 10.9%, with no significant difference across the three treatment arms in the study. Pre-treatment serum albumin levels were the only significant predictor of recurrence, with lower levels associated with a higher likelihood of recurrence.

Aims and Objectives

Aim of the study:

To describe the clinico-epidemiological profile of patients developing Drug Induced Liver Injury (DILI) who are receiving anti-tubercular therapy (ATT).

Primary Objectives:

1. To Identify predictors of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT).
2. To construct a best-fit model for the prediction of the occurrence of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT).

Materials and Methods

Methodology

Study design:

The study was a case-control type of study conducted from February 2023 to August 2024.

Study setting:

Patients attending Outpatient Departments, hospitalised patients, patients attending Adverse Drug Reaction (ADR) centre and National Tuberculosis Elimination Programme (NTEP) centre.

Study population:

Patients taking Anti-tubercular therapy (ATT).

Inclusion criteria for the study:

1. Individuals over 18 years of age
2. Individuals on antitubercular therapy (ATT).
3. Consenting individuals

Exclusion criteria for the study:

1. Incomplete medical records

Operational Study Definitions:

1. Drug-induced liver injury DILI (case): Individuals on anti-tubercular therapy and having deranged AST/ALT (>3 times the upper limit of the normal value) with symptoms (nausea/vomiting/ lethargy/ jaundice, etc.)
2. Control: Individuals on anti-tubercular therapy from NTEP centre, AIIMS Bhopal, without developing DILI.

3. Antituberculosis therapy (ATT): Patients on conventional fixed-dose anti-tubercular combination therapy as per NTEP.
4. Tuberculosis: Microbiologically confirmed (CBNAAT / AFB / culture) **or** clinically diagnosed **(**presence of granulomas, high protein with lymphocytic pleocytosis or suggestive imaging).
5. Pulmonary TB: Microbiological or clinical tuberculosis with involvement of lung parenchyma
6. Extra pulmonary TB: Microbiological or clinical tuberculosis of all other sites, excluding lung parenchyma.
7. Disseminated TB: Tuberculosis at two or more non-contiguous sites.
8. Severe TB: Disseminated TB or TB (Pulmonary or extrapulmonary) requiring hospitalisation.
9. Socioeconomic status (Below Poverty Line-BPL): Individuals with ration card.
10. BMI (Body mass index): Defined as weight in kilograms divided by the square of the height in metres: weight/height^2 .
11. Chronic Liver Disease (CLD): Documented liver dysfunction (coagulopathy, transaminitis, hyperbilirubinemia, or hypoalbuminemia) for more than 6 months or radiologically diagnosed cirrhosis of the liver.
12. Hepatitis infection: Defined as ELISA positive for HBV(HbsAg) or HCV infection.
13. Alcohol consumption: Ongoing more than 2 drinks/week for at least one year.(33)
14. Diabetes mellitus: Defined as per the ADA 2024 guidelines, a fasting plasma glucose of 126 mg/dL or higher, a 2-hour plasma glucose of 200 mg/dL or higher during an oral glucose tolerance test, an HbA1c level of 6.5% or higher, or a random plasma glucose of 200 mg/dL or higher in individuals with symptoms of

hyperglycaemia. (34) Patients already taking oral hypoglycaemic agents or insulin were also considered diabetic individuals.

15. Hypertension: Defined as BP more than 140/90 (35) or patients already taking antihypertensive drugs.
16. HIV coinfection: Defined as NACO ICTC-positive patients or patients already taking Antiretroviral therapy.
17. Hepatotoxic drugs: Drugs with evidence of hepatoxicity as per the LiverTox® registry.(36)
18. Systemic fungal infection: aspergillosis and / or candidiasis and / or cryptococcosis and / or mucormycosis and / or pneumocystosis. (37)
19. Malignancy: Operationally defined as biopsy-proven or imaging or tumour marker positive malignancy (past history or active).
20. Fever: Defined as elevation of body temperature (>37.2°C/98.9°F in the morning and >37.7°C/99.9°F in the evening) in conjunction with an increase in the hypothalamic set point.(38)
21. Weight loss: Defined as unintentional loss in weight of at least 5% of the patient's usual body weight that occurs within the preceding 6 to 12 months, and that is not the expected consequence of treatment of a known illness.(39)
22. Night sweats: Defined as repeated episodes of very heavy sweating during sleep, heavy enough to soak night clothes or bedding.(40)
23. Shortness of breath: Defined as the subjective sensation of uncomfortable breathing comprised of various sensations of varying intensity.(41)
24. Lymph node enlargement: Defined > 1 cm in cervical area/axilla or > 2 cm in inguinal area.(42)

25. Localised collection: Defined as a collection of pus in a cavity formed from tissues that have been broken down.(43)
26. Infertility: Defined as a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.(44)
27. Abdominal discomfort: Defined as an unpleasant or painful sensation in the abdominal region.(45)
28. Altered sensorium: Defined as disorders of mental functioning ranging from slight confusion to coma.(46)
29. Skin findings: Including inflammatory papules or ulcers or nodules or pustules or verrucous plaques or any other type of lesion.(47)
30. Altered vision: Operationally defined as painful or painless blurring of vision with objective signs of ocular TB on examination.
31. Crepitation: Defined as audible crackles heard on auscultation.
32. Reduced air entry: Muffled breath sounds as a result of pleural effusion, pneumonia, chronic obstructive pulmonary disease collapse, pneumothorax or a mass.(48)
33. Abdominal tenderness: Defined as a type of pain that is experienced on pressure application to the abdomen. (49)
34. Neck rigidity: Defined as abnormal difficulty in bending the head forward due to spasm of neck and spinal muscles.(50)

Exposures:

In this case-control study, the exposures were classified into modifiable and non-modifiable categories.

Non-modifiable exposures: (1) Socioeconomic status: Above the Poverty Line (APL) or Below the Poverty Line (BPL), (2) Age, (3) Gender (4) Height, (5) Type of tuberculosis: Disseminated TB, Extrapulmonary TB (EPTB), Pulmonary TB (PTB), (6) Severity of TB

Modifiable exposures: (1) Weight, (2) Body Mass Index (BMI), (3) Comorbidities: Hypertension, Diabetes, Malignancy, Systemic fungal infections, Concomitant hepatotoxic medication (Antiretroviral therapy; ART), Oral steroids.

Sample size and sampling:

Because of the time-bound nature of the post-graduation study period, a feasible sample size was adopted with a convenient sampling strategy.

Ethics Statement: The Institutional Human Ethics Committee (IHEC) approved the study. The permission letter dated 28th Feb 2023 (Ref Number: AIIMS/BPL/IHECSR/July/22/PG/07) is enclosed. All study cases and controls were only included after obtaining written informed consent.

Study Procedure:

This study was conducted at AIIMS Bhopal between February 2023 and August 2024 after approval by The Institutional Human Ethics Committee (IHEC), Letter of permission dated 28th Feb 2023 (Ref Number: AIIMS/BPL/IHECSR/July/22/PG/07) is enclosed as already attached above.

The study employed a case-control design to investigate the clinical, biochemical, and microbiological characteristics of patients diagnosed with pulmonary, extrapulmonary, or disseminated tuberculosis (TB) who developed DILI.

All the cases and controls were provided Patient Information Sheet (annexure 2). Adequate time was provided for both cases and controls; all queries were addressed, ensuring that individuals understood the study's purpose, procedures, and their rights. Informed consent was obtained from all cases and controls before enrolment. Only those who provided written consent were included in the study.

Patients reporting to OPD, IPD, ADR centre, and NTEP centre with nausea, vomiting, lethargy or jaundice and ALT/AST levels greater than equal to 3 times of ULN were labelled as cases. Eighty such cases were screened, and finally, 60 cases were enrolled in the study after the application of exclusion criteria as already mentioned.

Each case was matched with two controls, as defined under the study definitions. Controls were identified from NTEP register. Controls were recruited for each case who were initiated on ATT within 7 days (either side) of initiation of ATT as in that particular case. We screened 135 controls, out of which 120 individuals consented to participate. All cases and controls received conventional ATT in a fixed-dose combination, as per NTEP.

The following variables were collected for each case and control. Demographic profile (name in initials, age, gender), socioeconomic status (classified as Above the Poverty Line; APL or Below the Poverty Line; BPL), anthropometric measurements (height in meters, weight in kilograms, and BMI in kg/m^2) were recorded. Type of TB (pulmonary, extrapulmonary, and disseminated), severity of TB (severe or non-severe) and previous history of tuberculosis (including previous duration of ATT) were recorded. HIV co-infection and other comorbidity were recorded. Hepatic comorbidities, such as chronic liver disease (CLD), hepatitis B, hepatitis C, and a history of alcoholism, were assessed. In addition, extrahepatic comorbidities, including hypertension, diabetes, chronic kidney

disease (CKD), coronary artery disease (CAD), malignancy, and systemic fungal infections, were taken into account. Laboratory investigations included tubercular microbiology (AFB, CBNAAT, culture) haemoglobin levels, total leukocyte count (TLC), platelet count, urea, creatinine, total bilirubin (T. Bil), direct bilirubin (D. Bil), indirect bilirubin (I. Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). The occurrence of drug-induced liver injury (DILI) and the phase of ongoing anti-tuberculosis therapy (ATT) was also recorded. Various signs and symptoms exhibited by patients, such as fever, weight loss, night sweats, cough, shortness of breath, lymph node enlargement, localised collection, infertility, abdominal discomfort, altered sensorium, backache, skin findings, altered vision, crepitations, decreased air entry, abdominal tenderness, and neck rigidity were also documented. The details of the variables are attached as Annexure- 5.

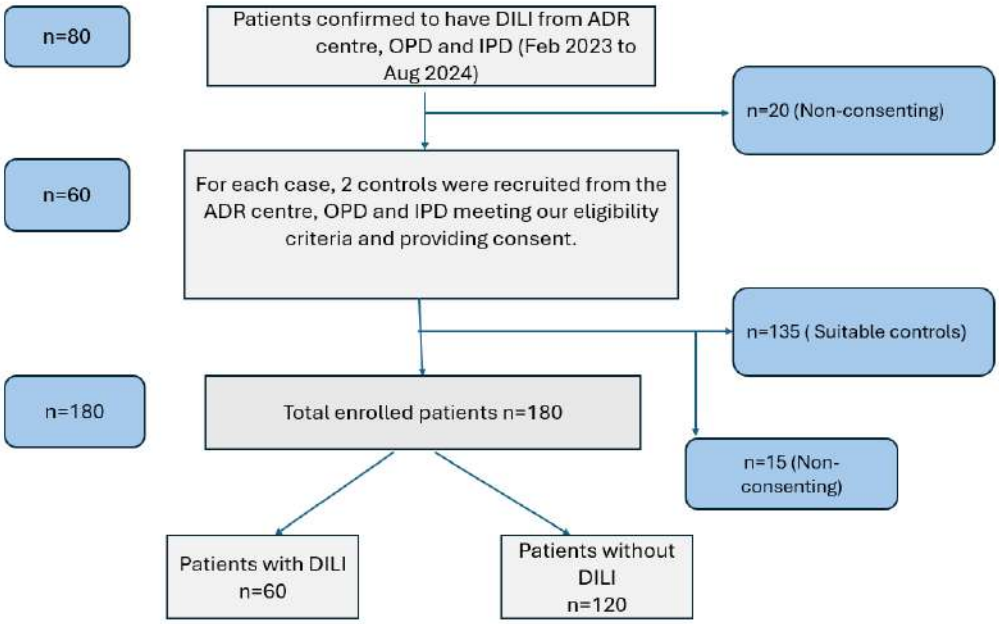
n=80
Patients confirmed to have DILI from ADR centre, OPD and IPD (Feb 2023 to Aug 2024)
n=20 (Non-consenting)
n=60
For each case, 2 controls were recruited from the ADR centre, OPD and IPD meeting our eligibility criteria and providing consent.
n=135 (Suitable controls)
n=180
Total enrolled patients n=180
n=15 (Non-consenting)
Patients with DILI n=60
Patients without DILI n=120

***Figure 1**: Enrolment details of the study participants*

The figure illustrates the flowchart of the study, showing the recruitment of 180 patients with tuberculosis (TB) on Anti-Tuberculosis Therapy (ATT) from OPD, IPD, ADR centres, and NTEP centre

Inclusion criteria for the study:

1. Consenting individuals
2. Individuals over 18 years of age
3. Individuals on antitubercular therapy

Exclusion criteria for study:

1. Incomplete patient data

Statistical Analysis:

Collected data as per the Case Record Form (CRF), was entered into an Excel sheet. The variables were coded numerically, and subsequently a code sheet was generated. The data was cleaned for outliers, duplications, and redundancies. Cleaned data was analysed by using R software (51) version 4.3.2; Oct 2023. The data was tested for normalcy and subsequently analysed non-parametrically wherever required. Frequencies and percentages were used for categorical variables, and medians with interquartile ranges (IQR) were employed for continuous variables. Fisher's exact test was applied to assess the relationship between categorical variables, and the Wilcoxon rank sum test was used for continuous variables. Univariate logistic regression was performed for each potential variable for the occurrence of DILI. A p -value of <0.05 was considered to be statistically significant. Those variables with a p-value of less than 0.05 from the univariate analysis were transposed for a multivariable logistic regression model to identify the independently associated variable for the prediction of DILI. A Generalized Linear Model was used for the multivariable logistic regression analysis. The best-fit model was identified with the Odds ratio (OR) with 95% Confidence interval (CI), Akaike information criterion (AIC) and Tjur's R value.

Results

Results:

This study was undertaken to describe the clinico-epidemiological profile of patients developing Drug Induced Liver Injury (DILI) who are receiving anti-tubercular therapy (ATT). The objectives of the study were to identify predictors of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT) and to construct a best-fit model for the prediction of the occurrence of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT).

This case-control (1:2) study was conducted as a post-graduation thesis at AIIMS Bhopal. The detailed methodology has already been discussed in the section on materials and methods. A total of 180 individuals were enrolled on the study after due consideration of inclusion and exclusion criteria.

Table 2 : Distribution of cases and controls (N = 180)

Characteristic	**Frequency% (N = 180)**
Occurrence of DILI	
Controls (controls)	120 (67%)
Case (cases)	60 (33%)

Out of these 180 individuals, 60 individuals were cases of DILI, and 120 individuals were recruited as controls. Out of the 60 Cases of DILI, 2 individuals (3.3%) had mortality and none among the controls.

Table 3 : Distribution of sociodemographic profile of cases and controls (N = 180)

Characteristic	Frequency% (N = 180)
Age(years)	36 (28, 55)
Socioeconomic status	
BPL (Below poverty line)	113 (63%)
APL (Above poverty line)	67 (37%)
Gender	
Male	100 (56%)
Female	80 (44%)
Height (m)	1.70 (1.63, 1.74)
Weight (kg)	54 (50, 59)
BMI (kg/m2)	18.92 (18.13, 20.31)

In the study, 37% of patients (67 individuals) were Above the Poverty Line (APL), while 63% (113 individuals) were Below the Poverty Line (BPL). The median age of the patients was 36 years, with an interquartile range (IQR) of 28 to 55 years. 44% of the patients were female and 56% were male. The median height was 1.70 meters (IQR: 1.63-1.74), and the median weight was 54 kg (IQR: 50-59). The median Body Mass Index (BMI) was 18.92 (IQR: 18.13-20.31).

Table 4 : Distribution of comorbidity profile in cases and controls (N = 180)

Characteristic	Frequency% (N = 180)
Comorbidities	
Hypertension	23 (13%)
Diabetes	12 (6.7%)
Systemic fungal infections	4 (2.2%)
Malignancy	2 (1.1%)
None	139 (77%)
Concomitant hepatotoxic medication	
ART	5 (2.8%)
Oral steroid	2 (1.1%)
None	173 (96%)

Hypertension was the most common comorbidity in 13% individuals followed by diabetes mellitus in 6.7% of individuals. 77% of individuals did not have any comorbidity. Regarding concomitant hepatotoxic medication, 2.8% of individuals (5 individuals) were receiving antiretroviral therapy, while 1.1% (2 individuals) were on oral steroids. 96% of individuals were not on any concomitant hepatotoxic medications.

Table 5 : Distribution of cases and controls based on signs and symptoms (N=180)

Characteristic	Frequency% (N = 180)
Fever	136 (76%)
Weight loss	64 (36%)
Cough	61 (34%)
Altered sensorium	40 (22%)
Abdominal discomfort	34 (19%)
Neck rigidity	33 (18%)
Abdominal Tenderness	26 (14%)
Backache	24 (13%)
Shortness of breath	21 (12%)
Decreased Air entry	21 (12%)
Lymph node enlargement	14 (7.8%)
Night sweats	12 (6.7%)
Crepitations	10 (5.6%)
Altered vision	7 (3.9%)
Skin findings	4 (2.2%)
Infertility	3 (1.7%)
Localized collection	1 (0.6%)

Fever was the most common presentation (76%), followed by weight loss (36%), cough (34%), altered sensorium (22%), abdominal discomfort (19%), neck rigidity (18%), backache (13%), decreased air entry (12%), shortness of breath (12%) and abdominal tenderness (14%).

Table 6: Distribution of cases and controls based on spectrum of TB (N = 180)

Characteristic	Frequency% (N = 180)
Type Of TB	
EPTB	120 (67%)
PTB	45 (25%)
Disseminated	15 (8.3%)
Microbiologic Evidence	44 (24%)
Severe TB	132 (73%)
Phase of ATT in which DILI occurred (N = 60)	
IP (Intensive phase)	49 (82%)
CP (Continuation phase)	11 (18%)

Out of total 180 individuals, 67% of patients (120 individuals) had EPTB, 25% (45 individuals) had PTB, and 8.3% (15 individuals) had disseminated TB.

Microbiological confirmation of TB was found in 24% (44 individuals). Severe TB was present in 73% of patients (132 individuals).

Among the 60 cases who developed drug-induced liver injury (DILI), 82% (49 individuals) experienced it during the intensive phase (IP) of anti-tuberculosis treatment (ATT), while 18% (11 individuals) experienced it during the continuous phase (CP).

Table 7: Distribution of cases and controls based on Lab parameters (N=180)

Characteristic	Frequency% (N = 180)
Haemoglobin (g/dl)	11.00 (10.08, 12.23)
TLC (per mm^3)	
4000-11000	153 (85%)
less than 4000	10 (5.6%)
more than 11000	17 (9.4%)
Platelet count (thousand/cumm)	285 (221, 359)
Urea (mg/dl)	27 (21, 34)
Creatinine (mg/dl)	0.98 (0.80, 1.13)
Total Bilirubin (mg/dl)	1.34 (1.09, 1.69)
Direct Bilirubin (mg/dl)	0.74 (0.60, 0.90)
Indirect Bilirubin (mg/dl)	0.60 (0.49, 0.90)
AST (IU/L)	51 (41, 178)
ALT (IU/L)	50 (41, 167)
Albumin (g/dl)	3.20 (2.97, 3.50)
ALP (IU/L)	50 (40, 89)
GGT (IU/L)	48 (41, 58)

The median Hb level was 11.00 g/dL (IQR: 10.08-12.23). TLC was within the normal range (4000-11000/mm³) in 85% of patients, below 4000/mm³ in 5.6%, and above 11000/mm³ in 9.4%. The median PLT count was 285,000/cumm (IQR: 221,000-359,000). Median urea levels of 27 mg/dL (IQR: 21-34), and creatinine was 0.98 mg/dL (IQR: 0.80-1.13). The median T. Bil was 1.34 mg/dL, D. Bil 0.74 mg/dL, and I. Bil 0.60 mg/dL. AST levels were 51 U/L (IQR: 41-178), ALT was 50 U/L (IQR: 41-167), albumin was 3.20 g/dL (IQR: 2.97-3.50), ALP was 50 U/L (IQR: 40-89), and GGT was 48 U/L (IQR: 41-58).

Table 8: Distribution of cases and controls based on history of previous ATT intake (N=180)

Characteristic	Frequency% (N = 180)
History of ATT intake	10 (5.6%)
History of DILI during previous ATT intake	9 (5.0%)
Duration of ATT at which DILI occurred during previous treatment (N=9)	
0-60 days	2 (1.1%)
61-180	5 (2.8%)
more than 180 days	2 (1.1%)

5.6% (10 individuals) had a history of anti-tuberculosis treatment (ATT) intake. The duration of ATT intake during previous treatment was 61-180 days in 5 individuals followed by 0-60 days in 2 individuals and more than 180 days in 2 individuals.

Out of 10 individuals with prior history of ATT intake, 9 individuals had a history of drug-induced liver injury (DILI) during previous ATT intake.

Table 9: Distribution of sociodemographic characteristics among cases and controls (N = 180)

Characteristic	Case, N = 60[1]	Controls, N= 120[1]	p-value[2]
Age (Years)	37 (28, 52)	36 (28, 55)	>0.9
Gender			
Male	35 (58%)	65 (54%)	0.6
Female	25 (42%)	55 (46%)	
BMI (Kg/m2)	19.48(17.77, 21.96)	18.82(18.21, 19.81)	0.13
Socioeconomic status			
BPL (Below the poverty	33 (55%)	80 (67%)	0.13
APL (Above the poverty	27 (45%)	40 (33%)	

[1]Median (IQR); N (%), [2]Wilcoxon rank sum test; Pearson's Chi-squared test

The cases had a median age of 37 years (IQR: 28-52) and comprised 42% females and 58% males. The median BMI in the cases was slightly higher at 19.48 (IQR: 17.77-21.96). Among the cases, 45% (27 individuals) were APL, whereas 55% (33 individuals) were BPL.

The controls had a median age of 36 years (IQR: 28-55), with 46% females and 54% males. The median BMI among the control was 18.82 (IQR: 18.21-19.81). 33% (40 individuals) among the control were APL, while 67% (80 individuals) were BPL. Statistical analyses revealed no significant differences between all these socio demographic groups among the cases and controls.

Table 10: Distribution of comorbidities among cases and controls (N = 180)

Characteristic	Case, N = 60[1]	Controls, N =	p-value[2]
CLD (Chronic Liver Disease)	5 (8.3%)	0 (0%)	**0.004**
Status of hepatitis infection			0.11
Hepatitis B	1 (1.7%)	0 (0%)	
Hepatitis C	1 (1.7%)	0 (0%)	
No	58 (97%)	120 (100%)	
Alcoholism	10 (17%)	36 (30%)	0.053
HIV Co-infection	5 (8.3%)	0 (0%)	**0.004**
Comorbidities			**<0.001**
Diabetes	3 (5.0%)	9 (7.5%)	
Hypertension	1 (1.7%)	22 (18%)	
Malignancy	2 (3.3%)	0 (0%)	
Systemic fungal infections	4 (6.7%)	0 (0%)	
None	50 (83%)	89 (74%)	
Concomitant hepatotoxic medication			**<0.001**
ART	5 (8.3%)	0 (0%)	
Oral steroid	2 (3.3%)	0 (0%)	
No	53 (88%)	120 (100%)	

***[1]* N (%); *[2]* Fisher's exact test; Pearson's Chi-squared test**

None of the Controls (N = 120) had Chronic Liver Disease (CLD), while 8.3% (5 individuals) in the Cases (N = 60) had CLD (p = 0.004). Hepatitis B and C infections were present in 1.7% (1 individual each) of the Cases. Alcoholism was reported in 17% in the Cases and 30% of the Controls without any statistical significance. HIV co-infection was significantly associated with DILI; as in 8.3% among Cases but none among Controls (p = 0.001). ART intake was statistically significant. Hypertension was significantly more common in the controls (18%) compared to the cases (1.7%) (p < 0.001).

Table 11: Distribution of symptoms and signs among cases and controls (N = 180)

Characteristic	Case, N = 60[1]	Controls, N = 120[1]	p-value[2]
Fever	46 (77%)	90 (75%)	0.8
Weight loss	34 (57%)	30 (25%)	**<0.001**
Cough	25 (42%)	36 (30%)	0.12
Altered sensorium	19 (32%)	21 (18%)	**0.031**
Neck rigidity	16 (27%)	17 (14%)	**0.041**
Shortness of breath	13 (22%)	8 (6.7%)	**0.003**
Night sweats	11 (18%)	1 (0.8%)	**<0.001**
Decreased air entry	10 (17%)	11 (9.2%)	0.14
Abdominal discomfort	9 (15%)	25 (21%)	0.3
Abdominal tenderness	9 (15%)	17 (14%)	0.9
Crepitation	8 (13%)	2 (1.7%)	**0.003**
Backache	5 (8.3%)	19 (16%)	0.2
Lymph node	4 (6.7%)	10 (8.3%)	0.8
Altered vision	3 (5.0%)	4 (3.3%)	0.7
Infertility	1 (1.7%)	2 (1.7%)	>0.9
Skin findings	1 (1.7%)	3 (2.5%)	>0.9
Localised collection	0 (0%)	1 (0.8%)	>0.9

[1] N (%); [2] Pearson's, Chi-squared tests; Fisher's exact test

Weight loss was significantly frequent in the Cases (57%) compared to the Controls (25%), with a p-value of <0.001. Night sweats were also significantly common in the Cases (18%) than in the controls (0.8%) ($p < 0.001$). Shortness of breath was significantly higher among cases 22% Vs. 6.7% in the controls ($p = 0.003$). Altered sensorium was significantly higher among cases in 32% Vs. 18% in the controls ($p = 0.031$). Crepitations were significantly higher in cases 13% Vs. 1.7% in the controls ($p = 0.003$), and neck rigidity was more frequent in the Cases (27%) than the controls (14%) ($p = 0.041$).

However, symptoms such as fever, cough, and abdominal discomfort did not show any significant differences between the groups.

Table 12: Distribution of spectrum of TB among cases and controls (N = 180)

Characteristic	Case, N = 60[1]	Controls, N = 120[1]	p-value[2]
Type of TB			
EPTB	33 (55%)	87 (73%)	
PTB	18 (30%)	27 (23%)	**0.023**
Disseminated	9 (15%)	6 (5.0%)	
Microbiologic evidence	15 (25%)	29 (24%)	>0.9
Severe TB	45 (75%)	87 (73%)	0.7
Phase of ATT in which DILI occurred (N=60)			>0.9
IP (Intensive phase)	49 (82%)	0 (NA%)	
CP (Continuous phase)	11 (18%)	0 (NA%)	

[1] N (%); [2] Pearson's, Chi-squared tests; Fisher's exact test

Disseminated TB was significantly frequent among the cases (15%) compared to the controls (5%) (p = 0.023).

Microbiologic evidence was similar between the groups (24% in controls vs. 25% in cases, p > 0.9), as was the proportion of severe TB (73% in controls vs. 75% in cases, p = 0.7). 82% of the cases developed DILI during the intensive phase (IP) of anti-tuberculosis therapy (ATT), while 18% occurred in the continuous phase (CP).

Table 13: Distribution of laboratory parameters among the cases and controls (N = 180)

Characteristic	Case, N = 60[1]	Controls, N = 120[1]	p-value[2]
Haemoglobin (g/dl)	10.45 (9.38, 12.00)	11.30 (10.40, 12.30)	**0.001**
TLC (per mm^3)			**<0.001**
4000-11000	38 (63%)	115 (96%)	
less than 4000	7 (12%)	3 (2.5%)	
more than 11000	15 (25%)	2 (1.7%)	
Platelet-count (thousand/cumm)	262 (220, 344)	295 (223, 361)	0.7
Urea (mg/dl)	28 (21, 37)	26 (21, 32)	0.2
Creatinine (mg/dl)	0.90 (0.69, 1.10)	1.00 (0.88, 1.19)	**0.010**
Albumin (g/dl)	2.90 (2.40, 3.33)	3.40 (3.12, 3.60)	**<0.001**

[1] Median (IQR); N (%), [2] Wilcoxon rank sum test; Fisher's exact test

Low Haemoglobin levels was significantly associated with Cases (median 10.45 g/dl) in comparison to controls (median 11.30 g/dl) ($p = 0.001$). While measuring TLC, leucopoenia <4000 and Leucocytosis >11,000 were significantly more prevalent among the Cases ($p < 0.001$). Creatinine levels were significantly lower among the Cases (median 0.90 mg/dl) compared to the controls (median 1.00 mg/dl) ($p = 0.010$). Albumin levels were significantly lower among the Cases (median 2.90 g/dl) compared to the controls (median 3.40 g/dl) ($p < 0.001$). Platelet count and urea levels did not show significant differences between the two groups.

Table 14: Distribution of history of prior ATT intake among the cases and controls (N = 180)

Characteristic	Cases, N = 60[1]	Controls, N	p-value[2]
History of ATT intake	9 (15%)	1 (0.8%)	**<0.001**
Duration of ATT intake at			**<0.001**
0-60 days	2 (3.3%)	0 (0%)	
61-180	5 (8.3%)	0 (0%)	
more than 180 days	2 (3.3%)	0 (0%)	
None	51 (85%)	120 (100%)	
History of DILI during	9 (15%)	0 (0%)	**<0.001**

[1] N (%); [2] Fisher's exact test; Pearson's Chi-squared test

History of prior ATT intake was significantly associated with DILI among cases 15% Vs. 0.8% in the Controls ($p < 0.001$). A prior history of intake of ATT for 61-180 days was significantly associated with DILI cases in comparison to controls.

Table 15: Predictive model for development of DILI with ATT intake

Characteristic	**Model 1 (OR, 95% CI,**	**Model 2 (OR, 95% CI,**	**Model 3 (OR, 95% CI,**
Weight loss	4.92 (2.05, 12.5), <0.001	4.68 (2.12, 10.7),	5.42 (2.56, 12.0),
Night sweats	18.4 (2.60, 398), 0.014	—	—
Shortness of breath	5.68 (1.77, 18.9), 0.004	3.38 (1.01, 11.6), 0.048	3.15 (1.01, 10.1), 0.048
Altered sensorium	3.18 (0.63, 15.5), 0.15	—	—
Crepitations	2.79 (0.35, 28.9), 0.3	—	—
Neck rigidity	2.14 (0.42, 11.6), 0.4	—	—
Type of TB			
PTB	—	—	—
Disseminated	0.97 (0.19, 4.89), >0.9	—	—
EPTB	1.22 (0.45, 3.54), 0.7	—	—
Haemoglobin (g/dl)	—	0.87 (0.64, 1.17), 0.4	—
TLC (per mm3)			
4000-11000	—	—	—
less than 4000	—	5.03 (1.08, 28.2), 0.046	8.16 (1.87, 43.8), 0.007
more than 11000	—	22.4 (4.81, 188), <0.001	32.8 (7.92, 227), <0.001
Creatinine	—	0.88 (0.62, 1.51), 0.5	—
Albumin	—	0.32 (0.12, 0.81), 0.019	—
AIC	195.11	175.06	180.78
Tjur’s R	0.27	0.37	0.31

The best-fit model was model-2, identified with the Odds ratio (OR) with 95% Confidence interval (CI), Akaike information criterion (AIC) and Tjur’s R values as mentioned above.

Predictors in Model 2 can explain 37% of the factors that influence occurrence of DILI.

Discussion

Discussion:

This study was undertaken to identify predictors of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT) and to construct a best-fit model for the prediction of the occurrence of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT). This case-control (1:2) study was conducted at AIIMS Bhopal. The detailed methodology has already been discussed. A total of 180 individuals (60 cases and 120 controls) were enrolled into the study after due consideration of inclusion and exclusion criteria.

Previous literatures have documented many risk factors for the development of drug-induced liver injury (DILI) during anti-tuberculosis therapy (ATT). Oa M et al., in their study, found that out of 473 tuberculosis (TB) patients, 46 developed hepatitis, leading to a prevalence of drug-induced hepatitis at 9.7%. Significant risk factors for DILI in their study included HIV infection, extrapulmonary tuberculosis, lower serum albumin, and higher serum globulin. On binary logistic regression, HIV infection and extrapulmonary TB remained significant predictors.(52) Hu X et al. also documented a similar incidence of DILI Cases, 10.6%, in their cohort. We could not calculate the prevalence of DILI cases among the individuals taking ATT as our study was a case-control study, and our entry point was the identification of cases.

In our study, we observed that the median Body Mass Index (BMI) was 18.92 (IQR: 18.13-20.31), and leukopenia was prominent in patients who developed DILI. A study conducted by Hu X et al. () on 644 TB patients found that lower body mass index (BMI) and leukopenia were associated with higher rates of DILI. (53)

A study by Stefanescu et al. indicated that TB treatment improved haemoglobin levels in patients who responded to treatment. (32) This finding was consistent with our study

revealing lower haemoglobin levels in DILI cases 10.45g/dl (9.38, 12.00) vs controls 11.30g/dl (10.40, 12.30) with a significant p-value. Lower haemoglobin levels may be because of a prolonged inflammatory process and anaemia of chronic disease.

In our study, lower creatinine levels were associated with DILI, which may reflect poor muscle mass because of poor nutritional status. It is a well-known fact that deranged renal function predisposes patients to DILI. (29) This negative association between decreased creatinine and the development of DILI has not been published earlier to the best of our knowledge, which needs further study with a larger sample.

Kumar M et al. found that patients with tuberculous meningitis (TBM) who developed DILI had worse outcomes, including a higher mortality rate. Factors such as lower Glasgow Coma Scale (GCS) scores, systemic inflammatory response syndrome (SIRS), and elevated inflammatory markers were significant predictors of DILI. (54) Similarly, in our study, we also observed a higher incidence of DILI in patients with more severe forms of TB, such as disseminated TB and TB Meningitis.

In our study, Chronic Liver Disease (CLD) was a significant risk factor for developing DILI in univariate analysis, reinforcing the importance of frequent monitoring of liver function in these subgroups of individuals on ATT. Chronic liver disease (CLD) has been identified as a risk factor for DILI in patients receiving ATT in previous studies. In a study by Park et al., 19% of patients with CLD developed DILI, with chronic hepatitis posing a higher risk compared to compensated cirrhosis. However, cirrhosis itself was not an independent risk factor. (55) Similarly, Edwards et al. found that DILI requiring treatment modification occurred in 58.9% of patients with chronic hepatitis or cirrhosis, and treatment success was achieved in 97% of those who tolerated a rifamycin-based regimen. (56)

In our study, Hypertension was more common among controls than in cases, which was statistically significant. This negative association between hypertension and DILI cases has not been previously published to the best of our knowledge. We are unable to describe this negative association, which may or may not be a causal association.

In our study, individuals on anti retroviral therapy (ART) were at a higher risk of developing DILI, suggesting that the combination of ART and ATT may predispose them to DILI. Similar to our study, Tedla Z et al. found that patients on ART, particularly those with CD4 counts below 200 or on nevirapine-based regimens, had a higher risk of INH-associated hepatitis. Tedla Z et al also documented that alcohol use and older age also contributed to the risk. (57)

The reintroduction of ATT following DILI presents its own challenges. We observed in our study that there was a significantly high recurrence (9 out of 9 cases) rate of DILI in patients who experienced DILI previously. In a study by Sharma SK et al., (25) the recurrence of DILI upon reintroduction varied, with rates between 10.9% and 18% depending on the regimen used. Factors associated with the recurrence of DILI included female sex, lower albumin levels, younger age, and higher bilirubin, as per the study of Sharma SK et al. The incremental approach in drug reintroduction reduced recurrence rates, as advocated by the American Thoracic Society (ATS), demonstrating superior outcomes compared to other approaches. (27)

As described in Table 15: Predictive model for the development of DILI with ATT intake, our study revealed several significant predictors of DILI, including weight loss, shortness of breath, total leukocyte count (TLC), and serum albumin levels. These findings are in line with previous research, which has explored the multifactorial nature of DILI and its association with both clinical characteristics and laboratory markers.

1. Weight Loss as a Predictor of DILI

Weight loss, commonly seen in tuberculosis (TB) patients, was identified as a significant predictor of DILI in our study. This association is supported by literature emphasizing the nutritional vulnerability of TB patients. TB-related weight loss may reflect malnutrition or cachexia, conditions that can exacerbate hepatic vulnerability. The liver plays a key role in protein synthesis, detoxification, and nutrient metabolism; therefore, malnourished patients are less capable of detoxifying drugs, including anti-TB medications. This could explain the higher incidence of DILI in individuals.

Warmelink et al conducted a study in 192 TB patients of which 16.1% experienced drug-induced hepatotoxicity (DIH), leading to anti-TB treatment interruption. Significant risk factors for DIH were weight loss of 2 kg or more during treatment (OR 211), hepatitis C infection (OR 19.6), age over 60 (OR 18.5), and multi-drug-resistant TB (OR 8.2). Patients who lost weight were more likely to interrupt treatment early, with 67% discontinuing within the first 15 days. Pyrazinamide doses were lower in those who developed DIH. (58)

Moreover, weight loss may be a marker of advanced disease or poor nutritional status, both of which compromise liver function. Lower baseline nutritional status can impair the liver's ability to regenerate and detoxify, leading to heightened vulnerability to hepatotoxic insults from ATT. Thus, the observed association between weight loss and DILI is consistent with the theory that malnutrition exacerbates the hepatotoxic potential of ATT drugs like isoniazid and rifampin.

2. Shortness of Breath and DILI

Shortness of breath, typically not directly linked to liver injury, was also found to be a significant predictor of DILI in our study. This could be an indirect marker of severe TB

or systemic involvement, both of which could increase the physiological stress on the liver. Patients with extensive pulmonary and pleural involvement may have worse overall health status, including compromised liver function, due to the systemic inflammatory response or co-existing conditions such as hypoxia or a hepato-pulmonary syndrome-like illness, which can affect liver metabolism.

Senaratne et al conducted a study in 783 patients with TB. The majority of the cohort (92.1%) had pulmonary TB. A smaller fraction (7.9%) had extra-pulmonary TB. DILI developed in 9.5% (74 patients) of the total population, with most cases (58%) occurring within the first two weeks of the intensive phase of anti-TB treatment. (31)

Singla et al observed 237 patients with anti-TB drug-induced hepatitis (DIH), with 175 included for analysis. Among DILI cases, those with pulmonary TB had significantly more severe chest radiograph findings compared to controls (82.2% vs. 54.7%, P<0.01). Clinically such patients may have severe crepitations on examination, as indicated by a significant p value of the finding in the univariate analysis in our study. Extrapulmonary TB was more prevalent in DILI cases (55.4%) than in controls (33.6%). Risk factors for DIH included age over 35, low mid-arm circumference (MAC < 20 cm), and hypoalbuminemia (albumin < 3.5 g/dL). Peak liver function derangements included high serum bilirubin and elevated AST/ALT levels. Most DILI cases were on a daily regimen, with a median onset of 23 days. (22)

In such cases, the liver is often tasked with metabolizing multiple drugs while also handling the increased metabolic demands imposed by systemic illness. This dual burden could predispose such patients to hepatic injury, especially during the early intensive phase of ATT.

3. Total Leukocyte Count (TLC) and DILI

Our study found a significant association between both elevated and decreased total leukocyte count (TLC) with development of DILI. TLC is a marker of systemic inflammation, and its elevation could reflect the body's inflammatory response to both the tuberculosis infection and the hepatotoxicity induced by ATT. Leukopenia is also a marker of severe infection and should be looked at with equal concern.

In a study by Ji S et al, an elevated neutrophil count was identified as a significant risk factor for developing drug-induced liver injury (DILI) in patients undergoing anti-TB treatment. Stepwise regression analysis revealed higher neutrophil counts were associated with a 2.145 times greater likelihood of developing DILI (OR 2.145 [1.078–4.700], p = 0.013). Neutrophilia may reflect as a rise in total leucocyte count (leucocytosis).(4)

In a study by Ştefanescu et al of 90 newly diagnosed pulmonary TB patients, 63 achieved negative culture conversion after 2 months of anti-TB treatment. Significant reductions in key haematological parameters were observed between baseline (T0) and post-treatment (T2), including WBC, neutrophils (NEU), monocytes (MON), and platelets (PLT), alongside lower systemic inflammatory indices (SII, NLR, PLR, MLR). Among 27 patients who remained culture-positive, increases in Hb, RDW-CV, and RDW-SD were observed. Spearman’s correlation revealed strong associations between SII, NEU, and PLT. Logistic regression showed the best predictive model (AUC: 0.735) combining multiple parameters, including age, Neutrophil count, and Systemic Inflammatory Index, for diagnosing culture status after 2 months. This shows that there is a relationship between neutrophils and microbiological evidence of tuberculosis, reflecting that in culture-positive TB, there is a strong possibility of neutrophilia and leucocytosis. (32)

In a study by Aljohaney AA et al of 291 tuberculosis patients, leukopenia emerged as a key predictor of inpatient mortality, particularly in those with pulmonary, extrapulmonary,

or both forms of TB. Patients with leukopenia had a higher risk of poor outcomes, including death. Along with other factors like age and comorbidities, leukopenia contributed significantly to the likelihood of mortality in hospitalised TB patients. (59)

In a study by Shishido Y et al, over a 20-year period, agranulocytosis due to anti-tuberculosis drugs occurred in 4 out of 6,400 patients at an incidence rate of 0.06%. Patients developed agranulocytosis 1-3 months into chemotherapy involving drugs like rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin. Most recovered after discontinuing the drugs and receiving granulocyte colony-stimulating factor (G-CSF), though one patient died due to complications. Similar global cases suggest an allergic mechanism, often with eosinophilia and skin eruptions. (7) This may indicate that concomitant leukopenia may not be a direct risk factor for DILI but an adverse effect of ATT.(60)

Additionally, inflammation-induced alterations in cytokine levels, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can exacerbate liver injury by promoting oxidative stress and impairing hepatocyte regeneration. TLC may serve as an indirect marker of this heightened inflammatory state, providing an explanation for the association between higher TLC and an increased risk of DILI.

4. Serum Albumin as a Predictor of DILI

The role of serum albumin as a predictor of DILI is well-supported by existing literature. Albumin, is a key protein synthesized by the liver, reflects the functional reserve of the liver. In our study, low serum albumin levels were associated with a higher risk of DILI.

In a prospective cohort study of 339 patients undergoing anti-TB treatment, Mahmood et al critically evaluated albumin levels as a potential risk factor for hepatotoxicity. Over

90% of patients had albumin levels below 3.5 g/dL, indicating lean body mass, which was statistically significant (P<0.01) and predisposed them to liver injury. (6)

In a study by Rajmani SS et al, hypoalbuminemia emerged as a significant risk factor for the development of drug-induced liver injury (DILI) in patients undergoing anti-tuberculosis treatment (ATT), with an odds ratio (OR) of 1.92. This indicates that patients with lower albumin levels are nearly twice as likely to experience DILI compared to those with normal albumin levels. (21)

In the study of drug-induced hepatotoxicity (DIH) among patients receiving anti-tuberculosis (ATT) treatment by Singla et al, serum albumin levels emerged as a significant factor. Patients with DIH exhibited notably lower baseline serum albumin levels compared to controls, averaging 3.85 g/dl versus 4.27 g/dl, with a statistically significant difference (P < 0.001). Among the 175 patients diagnosed with DIH, an alarming 91% had serum albumin levels below the acceptable threshold of 3.5 g/dl, indicating a high prevalence of hypoalbuminemia. At the time of DIH diagnosis, the average serum albumin level further declined to 3.56 g/dl, reflecting a compromised nutritional status. Both univariate and multivariate logistic regression analyses identified hypoalbuminemia as a significant predictor for the occurrence of DIH, highlighting that patients with low serum albumin levels are at a higher risk for developing hepatotoxicity during ATT. (22)

In a cohort of 237 patients who developed drug-induced hepatotoxicity (DIH) while undergoing anti-tuberculosis (ATT) treatment, serum albumin levels emerged as a critical factor in predicting the recurrence of DIH. Following the exclusion of patients with long-term alcoholism, those on hepatotoxic medications, and HIV-positive individuals, 175 patients were randomized into three treatment arms after their liver functions stabilized.

Among these, the only statistically significant predictor for the recurrence of DIH was the pretreatment serum albumin level. Sharma et al found that patients who experienced a recurrence had a mean pretreatment serum albumin level of 3.39 g/dl, notably lower than the 3.91 g/dl observed in patients who successfully tolerated the reintroduction of anti-TB drugs ($P < 0.01$). (25)

Albumin plays a crucial role in maintaining oncotic pressure and binding to various drugs, facilitating their transport and metabolism. Lower albumin levels indicate a compromised liver, which may be less efficient in metabolizing hepatotoxic drugs. Furthermore, hypoalbuminemia is often a marker of malnutrition or chronic liver disease, both of which increase susceptibility to DILI.

5.Timeline for development of DILI:

Our study found that most DILI cases (82%) occurred during the intensive phase (IP) of ATT. This phase involves higher doses of hepatotoxic drugs, such as isoniazid, rifampin, pyrazinamide, and ethambutol, which are known to stress the liver. The concentration and potency of these drugs during the intensive phase can overwhelm the liver's detoxification capacity, leading to the development of DILI.

Latief et al reported that 8.4% of tuberculosis patients on ATT developed DILI, with early manifestations occurring in 62.5% of cases. (20) Raj Mani SS et al. found that 76.7% of DILI cases occurred within the first two months of starting ATT. The study indicated that patients on a daily regimen had a higher incidence of DILI, particularly in the initial stages of treatment.(21) WV Senaratne et al. noted that 9.5% of patients developed anti-tuberculosis drug-induced hepatotoxicity, primarily within the first two weeks of treatment.(31) Sharma SK et al reported a median latency period of 23 days for the development of DILI among the 237 patients studied, with a median normalization time

of 18 days following successful management. (25) Singla R et al indicated that the median onset of DILI was observed at 23 days, aligning with the findings of Sharma et al. (22)

The earlier onset of DILI during ATT, may be explained by increased number of drug burden, combined with the metabolic demands of fighting an active infection, may predispose patients to hepatotoxicity during this early phase. Identifying patients at higher risk during the intensive phase is critical for early intervention, such as dose adjustment or close monitoring.

Although previous studies try to correlate microbiological evidence and risk of DILI development. (31) Interestingly, in our study, microbiological evidence of TB was present in only 24% of total cases and controls, yet a majority developed DILI. This suggests that the presence of microbiological evidence may not directly correlate with the risk of DILI. Instead, the systemic burden of disease, particularly in severe TB, could play a more prominent role in predisposing patients to liver injury.

DILI and Mortality:

In our study, which included 60 patients with DILI, the all-cause mortality rate was 3.3%, while no mortality was reported in the control group. A study on drug-induced liver injury (DILI) association with mortality was done by Rathi et al (19). Out of the 82 patients, 13 deaths occurred, with 8 being directly attributed to liver failure or complications, indicating a substantial burden of liver-related mortality in this cohort. Antitubercular therapy (ATT) DILI was associated with a significantly higher liver-related mortality rate of 17.5%, compared to 2.4% in patients with DILI from other drugs ($P = 0.02$).

Limitations of study**:**

1. Sample Size: Because of time-bound nature of Postgraduate study, we anticipated a feasible sample size during the study period. Our study included 180 individuals (60 cases and 120 controls), a larger sample size would provide more robust statistical power and enable more definitive conclusions. 2. Single-Centre Design: As this study was conducted at a single centre, the results may not entirely represent the diverse populations across different geographical regions.

3. Lack of Follow-up Duration: After identification of DILI cases, they were matched for controls and various variables were documented at that point of time. This study was not designed for follow up. However, as per the NTEP registry the mortality data has been analysed and presented under the section of result and discussion.

4. One limitation of our study is the absence of a formal causality assessment method, such as the Roussel Uclaf Causality Assessment Method (RUCAM), to systematically evaluate whether the liver injury observed in our patients was directly attributable to Anti-Tuberculosis Therapy (ATT).

5. Unmeasured Confounding Variables: Several potential confounding factors, such as genetic predispositions, alcohol intake, and concomitant use of other hepatotoxic drugs, were not fully accounted for. These factors may influence the risk of developing DILI and should be considered in future research.

6. Reliance on Clinical and Biochemical Markers: The study primarily relied on clinical and biochemical markers, such as albumin and total leukocyte count, without incorporating advanced imaging or liver biopsy data. More precise diagnostic tools could improve the detection and classification of DILI.

7. Microbiological Evidence: The relatively low percentage of cases and controls with microbiological evidence of TB (24%) limits the study's ability to explore associations between microbiologically confirmed TB and DILI risk. Including a larger proportion of microbiologically confirmed cases might yield different findings.

8. Liver Function at Baseline: The study did not assess baseline liver function comprehensively before the initiation of ATT. A more thorough evaluation of liver health at the outset of treatment could have clarified whether pre-existing liver conditions contributed to the development of DILI.

5. Unmeasured Confounding Variables: Several potential confounding factors, such as genetic predispositions, quantity and quality of alcohol intake, and concomitant use of other hepatotoxic drugs, were not fully accounted for.

6. Liver Function at Baseline: The study did not assess baseline liver function comprehensively before the initiation of ATT as per NTEP. A more thorough evaluation of liver health at the outset of treatment would have been helpful for better understanding.

Conclusion

Conclusion:

This time bound case control (1:2) study was undertaken to identify predictors of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT) and to construct a best-fit model for the prediction of the occurrence of Drug-Induced Liver Injury (DILI) in patients receiving anti-tubercular therapy (ATT) within the limitation as described above.

Univariate analysis revealed that several factors were significantly associated with DILI cases. These included chronic liver disease, HIV coinfection, ongoing ART, weight loss, altered sensorium, neck rigidity, shortness of breath, night sweats, crepitations, disseminated TB, TB meningitis, low haemoglobin, leukopenia, leucocytosis, low albumin, and a history of previous ATT intake or ATT-induced DILI. A negative association of DILI was seen with serum creatinine and hypertension.

However, the best-fit predictive model on logistic regression analysis identified weight loss, shortness of breath, leukopenia, leucocytosis, and low serum albumin has a better predictive value for identifying DILI among individuals receiving anti-tubercular therapy.

Earlier published variables such as female gender, hepatitis coinfection, creatinine, age, etc, could not associated with the development of DILI among individuals receiving anti-tubercular therapy.

Summary**:**

This case-control study (1:2) aimed to identify predictors of drug-induced liver injury (DILI) in patients receiving anti-tubercular therapy (ATT) and develop a predictive model. Logistic regression analysis identified weight loss, shortness of breath, leukopenia, leucocytosis, and low serum albumin as significant predictors of DILI. These clinical and laboratory markers demonstrated strong predictive value, allowing for the early identification of individuals at higher risk of developing DILI during ATT. The study underscores the need for vigilant monitoring of these factors to prevent or manage DILI in patients undergoing tuberculosis treatment.

References

1. Annual Reports – Central Tuberculosis Division [Internet]. [cited 2024 Aug 26]. Available from: https://tbcindia.mohfw.gov.in/annual-reports/

2. National Strategic Plan 2017-2025 for TB Elimination in India – Central Tuberculosis Division [Internet]. [cited 2024 Aug 26]. Available from: https://tbcindia-wp.azurewebsites.net/national-strategic-plan-2017-2025-for-tb-elimination-in-india/

3. Saha A, Shanthi F.X. M, Winston A. B, Das S, Kumar A, Michael JS, et al. Prevalence of Hepatotoxicity From Antituberculosis Therapy. J Prim Care Community Health. 2016 Jul;7(3):171–4.

4. Ji S, Lu B, Pan X. A nomogram model to predict the risk of drug-induced liver injury in patients receiving anti-tuberculosis treatment. Front Pharmacol. 2023;14:1153815.

5. Patterson B, Abbara A, Collin S, Henderson M, Shehata M, Gorgui-Naguib H, et al. Predicting drug-induced liver injury from anti-tuberculous medications by early monitoring of liver tests. J Infect. 2021 Feb 1;82(2):240–4.

6. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B uddin, Salkeen S. HEPATOTOXICITY WITH ANTITUBERCULOSIS DRUGS: THE RISK FACTORS.

7. Steele MA, Burk RF, DesPrez RM. Toxic Hepatitis with Isoniazid and Rifampin: A Meta-analysis. CHEST. 1991 Feb 1;99(2):465–71.

8. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. Ther Adv Gastroenterol. 2023 Mar 21;16:17562848231163410.

9. Brennan PN, Cartlidge P, Manship T, Dillon JF. Guideline review: EASL clinical practice guidelines: drug-induced liver injury (DILI). Frontline Gastroenterol. 2022 Jul;13(4):332–6.

10. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. BMC Infect Dis. 2017 Mar 24;17:231.

11. Anand A, Seth A, Paul M, Puri P. Risk Factors of Hepatotoxicity During Anti-tuberculosis Treatment. Med J Armed Forces India. 2006 Jan;62(1):45–9.

12. Puri P, Kaur N, Pathania S, Kumar S, Sharma PK, Sashindran VK. Antitubercular therapy induced liver function tests abnormalities in human immunodeficiency virus infected individuals. Med J Armed Forces India. 2017 Jan;73(1):12–7.

13. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis. Am J Respir Crit Care Med. 2003 Jun;167(11):1472–7.

14. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. J Clin Exp Hepatol. 2013 Mar;3(1):37–49.

15. Hussain Z, Kar P, Husain SA. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. Indian J Exp Biol. 2003 Nov;41(11):1226–32.

16. Das S, Behera SK, Xavier AS, Velupula S, Dkhar SA, Selvarajan S. Agreement Among Different Scales for Causality Assessment in Drug-Induced Liver Injury. Clin Drug Investig. 2018 Mar 1;38(3):211–8.

17. Agal S, Baijal R, Pramanik S, Pa[TEL] N, Gupte P, Kamani P, et al. Monitoring and management of antituberculosis drug induced hepatotoxicity. J Gastroenterol Hepatol. 2005;20(11):1745–52.

18. Sunil Kumar N, Remalayam B, Thomas V, Ramachandran TM, Sunil Kumar K. Outcomes and Predictors of Mortality in Patients With Drug-Induced Liver Injury at a Tertiary Hospital in South India: A Single-Centre Experience. J Clin Exp Hepatol. 2021;11(2):163–70.

19. Rathi C, Pipaliya N, Patel R, Ingle M, Phadke A, Sawant P. Drug Induced Liver Injury at a Tertiary Hospital in India: Etiology, Clinical Features and Predictors of Mortality. Ann Hepatol. 2017 May 1;16(3):442–50.

20. Latief M, Dar WR, Sofi N, Dar IA, Kasana B, Hussain M, et al. Novel risk factors and early detection of anti tubercular treatment induced liver injury—Looking beyond American Thoracic Society Guidelines. Indian J Tuberc. 2017 Jan 1;64(1):26–32.

21. Raj Mani SS, Iyyadurai R, Mishra AK, Manjunath K, Prasad J, Lakshmanan J, et al. Predicting antitubercular drug-induced liver injury and its outcome and introducing a novel scoring system. Int J Mycobacteriology. 2021;10(2):116–21.

22. Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, et al. Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. Indian J Med Res. 2010 Jul;132(1):81.

23. Moosa MS, Maartens G, Gunter H, Allie S, Chughlay MF, Setshedi M, et al. Rechallenge after anti-tuberculosis drug-induced liver injury in a high HIV prevalence cohort. South Afr J HIV Med. 2022 Jun 14;23(1):1376.

24. Soni H, Kumar-M P, Mishra S, Bellam BL, Singh H, Mandavdhare HS, et al. Risk of hepatitis with various reintroduction regimens of anti-tubercular therapy: a systematic review and network meta-analysis. Expert Rev Anti Infect Ther. 2020 Feb 1;18(2):171–9.

25. Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, et al. Safety of 3 Different Reintroduction Regimens of Antituberculosis Drugs after Development of Antituberculosis Treatment–Induced Hepatotoxicity. Clin Infect Dis. 2010 Mar 15;50(6):833–9.

26. Costiniuk CT, Gosnell BI, Manzini TC, Du Plessis CN, Moosa MYS. Tuberculous Drug-induced Liver Injury and Treatment Re-challenge in Human Immunodeficiency Virus Co-infection. J Glob Infect Dis. 2015;7(4):151–6.

27. Journal of cardiovascular Disease Researchs [Internet]. [cited 2024 Sep 6]. Available from: https://www.jcdronline.org/paper.php?slug=antituberculosis-drug-induced-liver-injury-clinical-profile-and-outcome-of-various-reintroduction-regimens

28. Zuberi FF, Zuberi BF, Bader N, Ali SK, Mumtaz F, Fatima T. Comparison of British and American Thoracic Societies' reintroduction guidelines for anti-tuberculous therapy induced liver injury. Eur Respir J [Internet]. 2013 Sep 1 [cited 2024 Sep 6];42(Suppl 57). Available from: https://erj.ersjournals.com/content/42/Suppl_57/P1606

29. Datta D, Rao IR, Prabhu AR, Nagaraju SP, Thunga G, Magazine R, et al. Effect of chronic kidney disease on adverse drug reactions to anti-tubercular treatment: a retrospective cohort study. Ren Fail. 46(2):2392883.

30. Lorent N, Sebatunzi O, Mukeshimana G, Van den Ende J, Clerinx J. Incidence and Risk Factors of Serious Adverse Events during Antituberculous Treatment in Rwanda: A Prospective Cohort Study. PLoS ONE. 2011 May 18;6(5):e19566.

31. Senaratne WV, Pinidiyapathirage MJ, Perera G, Wickremasinghe AR. Anti-tuberculosis drug inducd hepatitis – a Sri Lankan experience. Ceylon Med J [Internet]. 2009 Dec 7 [cited 2024 Oct 8];51(1). Available from: https://cmj.sljol.info/articles/10.4038/cmj.v51i1.1369

32. Ştefanescu S, Cocoş R, Turcu-Stiolica A, Mahler B, Meca AD, Giura AMC, et al. Evaluation of prognostic significance of hematological profiles after the intensive phase treatment in pulmonary tuberculosis patients from Romania. PLOS ONE. 2021 Apr 1;16(4):e0249301.

33. Yu A, Cooke AB, Scheffler P, Doonan RJ, Daskalopoulou SS. Alcohol Exerts a Shifted U-Shaped Effect on Central Blood Pressure in Young Adults. J Gen Intern Med. 2021 Oct;36(10):2975–81.

34. American Diabetes Association Professional Practice Committee, ElSayed NA, Aleppo G, Bannuru RR, Beverly EA, Bruemmer D, et al. Summary of Revisions: *Standards of Care in Diabetes—2024*. Diabetes Care. 2024 Jan 1;47(Supplement_1):S5–10.

35. New ESC Hypertension Guidelines recommend intensified BP targets and introduce a novel elevated blood pressure category to better identify people at risk for heart attack and stroke [Internet]. [cited 2024 Oct 7]. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/New-ESC-Hypertension-Guidelines-recommend-intensified-BP-targets-and-introduce-a-novel-elevated-blood-pressure-category-to-better-identify-people-at-risk-for-heart-attack-and-stroke

36. LiverTox [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2024 Oct 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/

37. Rautemaa-Richardson R, Richardson MD. Systemic fungal infections. Medicine (Baltimore). 2017 Dec 1;45(12):757–62.

38. Chapter 30: Fever, Hyperthermia, and Rash | Harrison's Manual of Medicine [Internet]. [cited 2024 Oct 8]. Available from: https://harrisons.unboundmedicine.com/harrisons/view/Harrisons-Manual-of-Medicine/623164/all/Chapter_30:_Fever__Hyperthermia__and_Rash?refer=true

39. Bosch X, Monclús E, Escoda O, Guerra-García M, Moreno P, Guasch N, et al. Unintentional weight loss: Clinical characteristics and outcomes in a prospective cohort of 2677 patients. Wu WCH, editor. PLOS ONE. 2017 Apr 7;12(4):e0175125.

40. Mayo Clinic [Internet]. [cited 2024 Oct 8]. Night sweats. Available from: https://www.mayoclinic.org/symptoms/night-sweats/basics/definition/sym-20050768

41. Hashmi MF, Modi P, Basit H, Sharma S. Dyspnea. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Oct 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499965/

42. Merck Manual Professional Edition [Internet]. [cited 2024 Oct 8]. Lymphadenopathy - Cardiovascular Disorders. Available from: https://www.merckmanuals.com/professional/cardiovascular-disorders/lymphatic-disorders/lymphadenopathy

43. Abscess | Definition, Causes, & Treatment | Britannica [Internet]. 2024 [cited 2024 Oct 8]. Available from: https://www.britannica.com/science/abscess

44. Infertility [Internet]. [cited 2024 Oct 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/infertility

45. Healthgrades [Internet]. 2014 [cited 2024 Oct 8]. Possible Causes for Abdominal Discomfort. Available from: https://www.healthgrades.com/right-care/symptoms-and-conditions/abdominal-discomfort

46. Evaluation of altered mental status - Differential diagnosis of symptoms | BMJ Best Practice US [Internet]. [cited 2024 Oct 8]. Available from: https://bestpractice.bmj.com/topics/en-us/843

47. Charifa A, Mangat R, Oakley AM. Cutaneous Tuberculosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Oct 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482220/

48. Education OM. Types of breath sound [Internet]. Oxford Medical Education. 2015 [cited 2024 Oct 8]. Available from: https://oxfordmedicaleducation.com/clinical-examinations/respiratory-examination/breath-sounds/

49. Abdominal tenderness: Causes, symptoms, and treatment [Internet]. 2019 [cited 2024 Oct 8]. Available from: https://www.medicalnewstoday.com/articles/325126

50. TheFreeDictionary.com [Internet]. [cited 2024 Oct 8]. neck rigidity. Available from: https://medical-dictionary.thefreedictionary.com/neck+rigidity

51. R: The R Project for Statistical Computing [Internet]. [cited 2024 Oct 15]. Available from: https://www.r-project.org/

52. Oa M, Ar F, S A, M KI. Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. Singapore Med J [Internet]. 2008 Sep [cited 2024 Oct 14];49(9). Available from: https://pubmed.ncbi.nlm.nih.gov/18830542/

53. Hu X, Zhang M, Bai H, Wu L, Chen Y, Ding L, et al. Antituberculosis Drug-Induced Adverse Events in the Liver, Kidneys, and Blood: Clinical Profiles and Pharmacogenetic Predictors. Clin Pharmacol Ther. 2018 Aug;104(2):326–34.

54. Kumar M, Kalita J, Tripathi A, Misra UK. Is drug-induced hepatitis related to the severity of tuberculous meningitis? Trans R Soc Trop Med Hyg. 2017 Nov 1;111(11):520–6.

55. Park WB, Kim W, Lee KL, Yim JJ, Kim M, Jung YJ, et al. Antituberculosis drug-induced liver injury in chronic hepatitis and cirrhosis. J Infect. 2010 Oct 1;61(4):323–9.

56. Edwards BD, Mah H, Sabur NF, Brode SK. Hepatotoxicity and tuberculosis treatment outcomes in chronic liver disease. J Assoc Med Microbiol Infect Dis Can. 8(1):64–74.

57. Tedla Z, Nyirenda S, Peeler C, Agizew T, Sibanda T, Motsamai O, et al. Isoniazid-associated Hepatitis and Antiretroviral Drugs during Tuberculosis Prophylaxis in HIV-infected Adults in Botswana. Am J Respir Crit Care Med. 2010 Jul 15;182(2):278–85.

58. Warmelink I, Hacken NH ten, Werf TS van der, Altena R van. Weight loss during tuberculosis treatment is an important risk factor for drug-induced hepatotoxicity. Br J Nutr. 2011 Feb;105(3):400–8.

59. Aljohaney AA. Mortality of patients hospitalized for active tuberculosis in King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Saudi Med J. 2018 Mar;39(3):267–72.

60. Shishido Y, Nagayama N, Masuda K, Baba M, Tamura A, Nagai H, et al. [Agranulocytosis due to anti-tuberculosis drugs including isoniazid (INH) and rifampicin (RFP)--a report of four cases and review of the literature]. Kekkaku. 2003 Nov;78(11):683–9.

Annexures

Annexures:

1. Data collection sheet
2. Participant information sheet (in English)
3. Participant information sheet (in Hindi)
4. Participant informed consent form
5. Master chart

Annexure 1

Data collection sheet

Initials of name

Socioeconomic status – APL/BPL

Age(years)

Gender

Height (m)

Weight (Kg)

BMI(Kg/m2)

Date of ATT initiation

Type Of TB - PTB/EPTB/Disseminated

Microbiologic Evidence – Yes/No

Severe TB – Yes/No

HIV co-infection – Yes/No

DILI -Yes/No

Phase of ATT in which DILI developed

Hepatic comorbidities – CLD/Hepatitis B/Hepatitis C/Alcoholism

Extrahepatic comorbidities – Hypertension/Diabetes/CKD/CAD/Malignancy/Systemic fungal infection

Duration of ATT intake during previous treatment(days) (If applicable)

Signs and symptoms - Fever/Weight loss/ Night sweats/ Cough/ Shortness of breath/ Lymph node enlargement/ Localised collection/ Infertility/ Abdominal discomfort/ Altered sensorium/ Backache/ Skin findings/ Altered vision/ Crepitations/ Decreased Air entry/ Abdominal Tenderness/ Neck rigidity

Lab Investigations – Hemoglobin / TLC / Platelet / Urea / Creatinine / T.Bil / D.Bil / I.Bil / AST / ALT / Albumin / ALP / GGT

Annexure 2

Participant Information Sheet (PIS)

Dear Sir/Madam,

You are invited to participate in a study titled "Predictors of Drug-Induced Liver Injury (DILI) Among Patients Receiving Anti-Tubercular Therapy."

Post-Graduate Student:

- Dr Shaurya Tewari
  Junior Resident, Department of General Medicine, AIIMS, Bhopal

Guide:

- Dr Sagar Khadanga
  Associate Professor, Department of General Medicine, AIIMS Bhopal

Co-Guides:

- Dr Abhishek Singhai	Assistant Professor, Department of General
- Dr Alkesh Khurana	Associate Professor, TB & Pulmonary Medicine,
- Dr Murali M	Associate Professor, Translational Medicine,
- Dr Abhijit Pakhare	Associate Professor, Community and Family

We appreciate your time and attention regarding the present study. Your participation is entirely voluntary. If you choose not to take part, you are free to decline without any need to provide a reason, and this will not affect your treatment. You can also withdraw from the study at any time without facing any disadvantage. If you agree to participate, we will ask you to sign a consent form.

PURPOSE OF THE STUDY

The purpose of this study is to identify factors that may predict liver injury (DILI) in patients receiving treatment for tuberculosis. Although liver injury can occur during treatment, the exact cause is not fully understood. Your participation will help us explore these factors.

WHAT WILL MY PARTICIPATION INVOLVE?

We will ask you some questions regarding your health, your treatment for tuberculosis, and any tests or investigations conducted by your doctor. We will record this relevant information as part of our study.

POSSIBLE BENEFITS AND RISKS

This is an observational study, meaning there is minimal risk to you. The benefit of this study is that by identifying factors linked to liver injury, we can improve understanding and potentially prevent similar complications in future patients.

YOUR RIGHTS

Participation is voluntary. You are free to decline participation or withdraw from the study at any time without any disadvantage. You will also have the right to access the information collected about you. Only authorized study investigators will have access to your data, and your privacy will be strictly maintained.

WHO DO I CONTACT FOR MORE INFORMATION?

If you have any questions or concerns about the study at any stage, please feel free to contact:

Student:

- DrShaurya Tewari (Mobile – 8433136326, email ID – tewarishaurya@gmail.com)
  Junior Resident (Academic), Department of General Medicine, AIIMS Bhopal

Ethics Committee Contact:

- DrShashank Purwar (Mobile – 7773010099, email ID – ihecpgr@aiimsbhopal.edu.in)
  Member Secretary, Institutional Human Ethics Committee-Student Research, AIIMS Bhopal

Annexure 3

संलग्नक-1: प्रतिभागी सूचना पत्रक (PIS)

प्रिय महोदय/महोदया,

आपको "एंटी-ट्यूबरकुलर थेरेपी प्राप्त कर रहे रोगियों में दवा-प्रेरित लिवर चोट (DILI) के पूर्वानुमानकर्ताओं" पर आधारित अध्ययन में भाग लेने के लिए आमंत्रित किया जाता है।

स्नातकोत्तर छात्र:

- डॉ. शौर्य तिवारी

जूनियर रेजिडेंट, सामान्य चिकित्सा विभाग, एम्स भोपाल

मार्गदर्शक:

- डॉ. सागर खादंगा

एसोसिएट प्रोफेसर, सामान्य चिकित्सा विभाग, एम्स भोपाल

सह-मार्गदर्शक:

- डॉ. अभिषेक सिंघाई	असिस्टेंट प्रोफेसर, सामान्य चिकित्सा विभाग, एम्स भोपाल
- डॉ. अलकेश खुराना	एसोसिएट प्रोफेसर, टीबी और पल्मोनरी मेडिसिन, एम्स भोपाल
- डॉ. मुरली एम	एसोसिएट प्रोफेसर, ट्रांसलेशनल मेडिसिन, एम्स भोपाल
- डॉ. अभिजीत पाखरे	एसोसिएट प्रोफेसर, सामुदायिक और पारिवारिक चिकित्सा, एम्स भोपाल

हम आपके समय और इस अध्ययन में आपकी रुचि की सराहना करते हैं। इस अध्ययन में भाग लेना पूरी तरह से स्वैच्छिक है। यदि आप भाग नहीं लेना चाहते हैं, तो इसके लिए आपको कोई कारण बताने की आवश्यकता नहीं है, और इसका आपके इलाज पर कोई प्रभाव नहीं पड़ेगा। आप किसी भी समय अध्ययन से बाहर निकल सकते हैं। यदि आप सहमति देते हैं, तो हम आपसे सहमति पत्र पर हस्ताक्षर करवाएँगे।

अध्ययन का उद्देश्य

इस अध्ययन का उद्देश्य यह पता लगाना है कि कौन से कारक ट्यूबरकुलोसिस उपचार के दौरान होने वाली लिवर चोट (DILI) की भविष्यवाणी कर सकते हैं। यद्यपि उपचार के दौरान लिवर चोट हो सकती है, इसके सही कारण अभी पूरी तरह से ज्ञात नहीं हैं। आपकी भागीदारी इन कारकों का पता लगाने में हमारी सहायता करेगी।

मेरे अध्ययन में भाग लेने में क्या शामिल होगा?

हम आपसे आपकी सेहत, ट्यूबरकुलोसिस के उपचार, और आपके डॉक्टर द्वारा किए गए किसी भी परीक्षण के बारे में कुछ प्रश्न पूछेंगे। हम इस जानकारी को अपने अध्ययन के हिस्से के रूप में दर्ज करेंगे।

अध्ययन के संभावित लाभ और जोखिम

यह एक अवलोकनात्मक अध्ययन है, इसलिए इसमें आपका जोखिम न्यूनतम है। इस अध्ययन का लाभ यह होगा कि लिवर चोट से संबंधित कारकों की पहचान करके, हम इसकी समझ में सुधार कर सकते हैं और भविष्य में इस तरह की जटिलताओं को रोक सकते हैं।

मेरे अधिकार

अध्ययन में भाग लेना स्वैच्छिक है। आप किसी भी समय बिना किसी नुकसान के अध्ययन में भाग लेने से इनकार कर सकते हैं या इसे छोड़ सकते हैं। आपको आपके बारे में एकत्रित की गई जानकारी तक पहुंचने का अधिकार भी होगा। केवल अधिकृत अध्ययन जांचकर्ता ही आपके डेटा तक पहुंच सकते हैं, और आपकी गोपनीयता को सख्ती से बनाए रखा जाएगा।

अधिक जानकारी के लिए किससे संपर्क करें?

यदि आपको अध्ययन के किसी भी चरण में कोई प्रश्न, चिंता या शिकायत हो, तो कृपया संपर्क करें:

स्नातक छात्र:

- डॉ. शौर्य तिवारी

मोबाइल न.: 8433136326

ई-मेल आईडी - tewarishaurya@gmail.com

जूनियर रेजिडेंट (अकादमिक), सामान्य चिकित्सा विभाग, एम्स भोपाल

नैतिक समिति संपर्क:

- डॉ. शशांक पुरवार

सदस्य सचिव, इंस्टीट्यूशनल ह्यूमन एथिक्स कमेटी-स्टूडेंट रिसर्च, एम्स भोपाल

(7773010099, ihecpgr@aiimsbhopal.edu.in)

Annexure 4

प्रतिभागी सूचना सहमति प्रपत्र

[PARTICIPANT INFORMED CONSENT FORM (PICF)]

अध्ययन के लिए प्रतिभागी का पहचान नंबर / Participant Identification Number for Study: ....

अनुसंधान का शीर्षक / Title of Project "Predictors of Drug Induced Liver Injury (DILI) among patients receiving anti-tubercular therapy.

छात्र शोधकर्ता का नाम / Name of Student Investigator Dr Shaurya Tewari
शोध मार्गदर्शक का नाम / Name of Thesis Guide : Dr Sagar Khadanga

मैंने संस्करण संख्या II..... दिनांक 20-08-2022 के सूचना पत्रक में दिए गए सभी तथ्यों को सावधानीपूर्वक पढ़ लिया है/ मुझे अपनी भाषा में स्पष्ट रूप से विस्तारपूर्वक समझा दिया गया है, और मैंने तथ्यों को पूर्णतः समझ लिया है। मैं पुष्टि करता/ करती हूँ, कि मुझे सवाल पूछने के अवसर प्रदान किए गए। The contents of the information sheet version II dated 20th August 2022 that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

मुझे इस अध्ययन की प्रकृति एवं उद्देश् य और इसके संभावित जोखिमों / लाभों तथा अध्ययन की अनुमानित अवधि एवं अन्य प्रासंगिक जानकारी के बारे में विस्तारपूर्वक समझा दिया गया है। मुझे पता है कि इस अध्ययन में मेरी भागीदारी स्वैच्छिक है तथा मैं इस अध्ययन से किसी भी समय बिना कोई कारण बताए, अपना नाम वापस लेने के लिए स्वतंत्र हूं और नाम वापस लेने पर मेरी चिकित्सा देखभाल या कानूनी अधिकारों पर कोई प्रभाव नहीं पड़ेगा। The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

मैं समझता/समझती हूं कि इस अनुसंधान में मेरी भागीदारी से मेरे बारे में एकत्र की गई जानकारी और मेरे चिकित्सीय दस्तावेजों के किसी भी भाग को एम्स के जिम्मेदार व्यक्तियों द्वारा ही देखा जाएगा। मैं इन व्यक्तियों को मेरे रिकॉर्ड प्राप्त करने की अनुमति प्रदान करता/ करती हूँ। I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

यदि प्रतिभागी बच्चा है, तो उसकी मौखिक या लिखित सहमति प्राप्त की गई है। If participant is child, his / her verbal or written assent has been obtained.

मैं उक्त अध्ययन में भाग लेने के लिए सहमत हूं। I agree to take part in the above study.

_____

(प्रतिभागी के हस्ताक्षर / बांए अंगूठे का निशान) (Signature / Left Thumb Impression)
दिनांक/Date.....स्थान/Place .....
प्रतिभागी का नाम/Name of the participant .....
पिता/पति/पत्नी का नाम /Son/Daughter/Spouse of.....
डाक का पूरा पता /Complete Postal Address .....

अगर अशिक्षित हो / *If illiterate,*

सूचना पत्र को प्रतिभागी को पढ़ा और समझाया गया है, और प्रश्न पूछने का अवसर दिया गया है। मैं पुष्टि करता हूं कि व्यक्ति ने स्वतंत्र रूप से सहमति दी है। The information sheet has been read and explained to the participant, and given the opportunity to ask questions. I confirm that the individual has given consent freely.

कानूनी रूप से स्वीकार्य प्रतिनिधि अथवा निष्पक्ष गवाह के हस्ताक्षर
Signature of Legally Acceptable Representative or impartial witness:
दिनांक / Date:
एलएआर अथवा निष्पक्ष गवाह का नाम / Name of LAR or impartial witness:
पता/Address:

प्रमाणित किया जाता है कि उक्त सहमति मेरी उपस्थिति में प्राप्त की गई ।
This is to certify that the above consent has been obtained in my presence.

_____

छात्र शोधकर्ता के हस्ताक्षर — दिनांक..... — स्थान.....
Signature of the Student Investigator — Date ..... — Place .....

कृपया ध्यान दें: सहमति प्रपत्र तीन प्रतियों में (1) रोगी के लिए, (2) शोधकर्ता, (3) संस्थान के लिए तैयार करें ।
Please note: Three copies should be made, for (1) Patient, (2) Researcher, (3) Institution

Master Chart

Annexure 5

Unique Id	occurrence of DILI	Socioeconomic status	Age	Gender	Height(m)	Height(cm)	Weight	BMI	CLD	Status of hepatitis infection	Alcoholism	HIV co infection	comorbidities	History of ATT	Duration of prior ATT	History of DILI	Concomitant hepatotoxic medication
ABPL_558	DILI positive	BPL	21	M	1.62	162	65	24.77	No	No	No	No	None	No	none	No	No
ABPL_559	DILI positive	BPL	23	F	1.58	158	50	20.03	No	No	No	No	None	No	none	No	No
ABPL_560	DILI positive	APL	60	F	1.54	154	50	21.08	No	No	No	No	None	No	none	No	No
ABPL_561	DILI positive	BPL	34	M	1.7	170	40	13.84	No	No	No	Yes	None	Yes	61-180	Yes	ART
ABPL_562	DILI positive	APL	71	M	1.66	166	62	22.50	No	No	No	No	None	No	none	No	No
ABPL_563	DILI positive	APL	43	F	1.6	160	52	20.31	No	No	No	No	None	No	none	No	No
ABPL_564	DILI positive	BPL	46	M	1.74	174	76	25.10	Yes	Hepatitis C	No	Yes	Systemic fungal infections	Yes	nore than 180 day	Yes	ART
ABPL_565	DILI positive	APL	23	F	1.61	161	35	13.50	No	No	No	No	None	Yes	61-180	Yes	No
ABPL_566	DILI positive	APL	55	F	1.62	162	48	18.29	No	No	No	No	None	No	none	No	No
ABPL_567	DILI positive	APL	90	F	1.58	158	42	16.82	No	No	No	No	None	Yes	0-60 days	Yes	No
ABPL_568	DILI positive	APL	28	F	1.59	159	76	30.06	No	No	No	No	None	No	none	No	No
ABPL_569	DILI positive	APL	31	F	1.64	164	58	21.56	No	No	No	No	None	Yes	61-180	Yes	No
ABPL_570	DILI positive	APL	28	F	1.62	162	60	22.86	No	No	No	No	None	No	none	No	No
ABPL_571	DILI positive	BPL	50	F	1.6	160	42	16.41	No	No	No	No	None	No	none	No	No
ABPL_572	DILI positive	BPL	62	M	1.72	172	80	27.04	No	No	No	No	None	No	none	No	No
ABPL_573	DILI positive	BPL	53	M	1.74	174	78	25.76	No	No	No	No	None	No	none	No	No
ABPL_574	DILI positive	BPL	62	F	1.62	162	54	20.58	No	No	No	No	Malignancy	No	none	No	No
ABPL_575	DILI positive	APL	36	M	1.72	172	70	23.66	No	No	No	No	None	No	none	No	No
ABPL_576	DILI positive	APL	38	F	1.62	162	100	38.10	No	No	No	No	None	No	none	No	No
ABPL_577	DILI positive	APL	65	M	1.72	172	64	21.63	No	No	No	No	Systemic fungal infections	No	none	No	Oral steroid
ABPL_578	DILI positive	APL	32	M	1.74	174	62	20.48	No	No	No	No	None	No	none	No	No
ABPL_579	DILI positive	BPL	31	M	1.74	174	66	21.80	No	No	No	No	None	No	none	No	No
ABPL_580	DILI positive	BPL	28	M	1.73	173	56	18.71	No	No	No	No	None	No	none	No	No
ABPL_581	DILI positive	BPL	41	M	1.67	167	73	26.18	No	No	No	No	Diabetes	No	none	No	Oral steroid
ABPL_582	DILI positive	APL	28	M	1.68	168	42	14.88	No	No	No	No	None	No	none	No	No
ABPL_583	DILI positive	APL	45	F	1.6	160	45	17.58	No	No	No	No	None	No	none	No	No
ABPL_584	DILI positive	BPL	21	F	1.62	162	70	26.67	No	No	No	No	None	No	none	No	No
ABPL_585	DILI positive	APL	64	M	1.74	174	52	17.18	No	No	No	Yes	None	Yes	nore than 180 day	Yes	ART
ABPL_586	DILI positive	BPL	21	F	1.66	166	58	21.05	No	No	No	No	None	Yes	61-180	Yes	No
ABPL_587	DILI positive	APL	85	M	1.76	176	58	18.72	No	No	No	No	None	No	none	No	No
ABPL_588	DILI positive	BPL	34	M	1.74	174	54	17.84	Yes	No	Yes	No	None	No	none	No	No
ABPL_589	DILI positive	BPL	25	M	1.72	172	52	17.58	No	No	Yes	No	None	No	none	No	No
ABPL_590	DILI positive	BPL	33	M	1.75	175	60	19.59	No	No	No	No	None	No	none	No	No
ABPL_591	DILI positive	BPL	40	M	1.74	174	60	19.82	Yes	No	Yes	No	Hypertension	No	none	No	No
ABPL_592	DILI positive	BPL	24	F	1.62	162	52	19.81	No	No	No	No	None	Yes	0-60 days	Yes	No
ABPL_593	DILI positive	APL	48	F	1.63	163	50	18.82	No	No	No	No	None	No	none	No	No
ABPL_594	DILI positive	BPL	39	M	1.7	170	54	18.69	No	No	No	No	None	No	none	No	No
ABPL_595	DILI positive	APL	46	F	1.58	158	42	16.82	Yes	Hepatitis B	No	No	None	No	none	No	No
ABPL_596	DILI positive	BPL	33	M	1.7	170	43	14.88	No	No	Yes	No	None	No	none	No	No
ABPL_597	DILI positive	BPL	55	M	1.74	174	54	17.84	No	No	No	No	Systemic fungal infections	No	none	No	No
ABPL_598	DILI positive	BPL	19	F	1.58	158	39	15.62	No	No	No	No	None	No	none	No	No
ABPL_599	DILI positive	BPL	22	M	1.58	158	48	19.23	No	No	No	No	Diabetes	No	none	No	No
ABPL_600	DILI positive	BPL	55	M	1.75	175	83	27.10	Yes	No	Yes	No	None	No	none	No	No
ABPL_601	DILI positive	APL	33	F	1.6	160	46	17.97	No	No	No	No	None	No	none	No	No
ABPL_602	DILI positive	BPL	22	F	1.59	159	47	18.59	No	No	No	No	None	Yes	61-180	Yes	No
ABPL_603	DILI positive	APL	25	M	1.71	171	58	19.84	No	No	Yes	No	None	No	none	No	No
ABPL_604	DILI positive	BPL	39	M	1.75	175	44	14.37	No	No	No	Yes	Systemic fungal infections	No	none	No	ART
ABPL_605	DILI positive	BPL	33	M	1.76	176	60	19.37	No	No	Yes	No	None	No	none	No	No
ABPL_606	DILI positive	BPL	76	F	1.64	164	56	20.82	No	No	No	No	Diabetes	No	none	No	No
ABPL_607	DILI positive	BPL	36	M	1.72	172	68	22.99	No	No	Yes	No	None	No	none	No	No
ABPL_608	DILI positive	BPL	51	M	1.73	173	70	23.39	No	No	Yes	No	None	No	none	No	No
ABPL_609	DILI positive	BPL	56	M	1.75	175	48	15.67	No	No	Yes	Yes	None	No	none	No	ART
ABPL_610	DILI positive	BPL	33	F	1.65	165	52	19.10	No	No	No	No	None	No	none	No	No
ABPL_611	DILI positive	APL	45	F	1.63	163	50	18.82	No	No	No	No	None	No	none	No	No
ABPL_612	DILI positive	APL	47	M	1.65	165	52	19.10	No	No	No	No	None	No	none	No	No
ABPL_613	DILI positive	APL	45	F	1.66	166	58	21.05	No	No	No	No	None	No	none	No	No
ABPL_614	DILI positive	APL	64	M	1.74	174	68	22.46	No	No	No	No	Malignancy	No	none	No	No
ABPL_615	DILI positive	APL	18	M	1.71	171	42	14.36	No	No	No	No	None	No	none	No	No
ABPL_616	DILI positive	BPL	18	M	1.73	173	48	16.04	No	No	No	No	None	No	none	No	No
ABPL_617	DILI positive	APL	20	M	1.74	174	55	18.17	No	No	No	No	None	No	none	No	No

Fever	Weight loss	Night sweats	Cough	Shortness of breath	Lymph node enlargement	Localised collection	Infertility	Abdominal discomfort	Altered sensorium	Backache	Skin findings	Altered vision	Crepititions	Decreased Air entry	Abdominal Tenderness	Neck rigidity	Type Of TB	Microbiologic Evidence	Severe TB	Hemoglobin	TLC	Platelet	Urea	Creatinine	T.Bil	D.Bil	I.Bil	AST	ALT	Albumin	ALP	GGT	Phase of ATT
No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	EPTB	No	Yes	12	4000-11000	255	24	0.8	3.00	1.8	1.2	473	629	3.6	110	35	CP
Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	No	13.1	4000-11000	225	17.9	0.7	0.56	0.14	0.42	154	155	4.17	94	38	IP
Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	Disseminated	No	Yes	9.3	more than 11000	177	49.5	1.12	14.40	12.9	1.5	268	320	2.8	180	62	IP
Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	PTB	Yes	Yes	8.87	4000-11000	225	29	0.86	5.28	3.46	1.82	1012	445	2.32	98	126	IP
Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	PTB	Yes	Yes	9.6	4000-11000	250	36	2.2	1.00	0.3	0.7	207	201	2.9	714	115	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	8.3	less than 4000	97	27	0.7	2.79	1.79	1	341	182	1.89	121	42	CP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	9.4	4000-11000	110	29.8	0.7	5.00	2.3	2.7	101	162	2.7	115	349	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	13.2	4000-11000	281	61.1	0.6	0.84	0.31	0.53	1038	357	3.86	82	52	CP
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	PTB	Yes	Yes	9.4	4000-11000	320	24	1.48	19.00	3	16	170	168	1.74	321	377	IP
Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	PTB	No	Yes	9.6	4000-11000	320	36.6	0.91	5.15	3.5	1.6	232	34	2.16	132	47	IP
Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	Yes	Yes	12.7	4000-11000	424	9.8	0.57	6.90	4.4	2.5	2736	924	3.6	67	61	CP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.8	more than 11000	441	20.97	0.36	4.25	2.88	1.37	277.2	228	2.6	361	947	CP
Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes	Disseminated	No	Yes	7.2	more than 11000	203	24	1.18	18.40	7.4	11	1592	781	3.6	153	35	IP
Yes	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes	Disseminated	Yes	Yes	8.2	4000-11000	262	43.3	0.63	8.54	4.8	3.7	206	171	2.24	199	137	IP
No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	PTB	No	Yes	9.9	more than 11000	783	18	1.09	1.19	0.75	0.44	590	548	3.1	101	73	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	No	13.8	4000-11000	321	13.1	0.98	0.77	0.27	0.5	319	203	4.41	137	85	IP
Yes	No	Yes	No	No	No	No	No	Yes	No	Yes	No	No	No	No	Yes	No	Disseminated	No	Yes	7.4	more than 11000	396	30.02	0.52	1.11	0.62	0.49	223	37	2.19	109	75	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.6	4000-11000	190	24	1.28	1.06	0.72	0.34	168	186	3.2	104	88	IP
No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	No	9	4000-11000	225	27	0.97	5.70	4.2	1.5	393	303	3.5	192	123	IP
Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No	PTB	Yes	Yes	10	more than 11000	592	31.5	1.15	2.13	2	0.13	510	64	3	89	97	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	No	12.3	4000-11000	500	32	1.01	0.84	0.27	0.57	171	252	4.3	253	54	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	14	more than 11000	318	27.24	0.64	6.81	3.89	2.92	351	550	2.48	135	284	IP
Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	PTB	No	Yes	11.4	less than 4000	511	22.67	0.99	4.90	3.3	1.6	666	857	2.5	183	215	IP
No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	EPTB	No	Yes	14.2	4000-11000	257	14	1.09	1.00	0.3	0.7	205	290	3.8	99	291	IP
Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Disseminated	No	Yes	12.2	4000-11000	251	14	0.7	1.50	1	0.5	203	360	3.77	67	20	IP
Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11.7	4000-11000	457	106	0.7	0.50	0.2	0.3	404	404	3.5	9.1	39	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.7	4000-11000	222	8.45	0.43	0.62	0.26	0.36	170	117	3.18	339	80	IP
No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.8	less than 4000	136	44	1.28	2.60	1.3	1.3	240	108	2.7	139	84	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.9	4000-11000	502	17.2	0.5	8.20	5.2	3	136	152	2.16	100	50	IP
No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10.2	more than 11000	343	30	1	0.95	0.31	0.66	177.4	62	3.13	165	27	IP
Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	6.8	more than 11000	172	9.7	0.6	14.93	8.11	6.82	151	36	2.78	270	210	IP
No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	10.5	4000-11000	404	17	0.6	0.70	0.3	0.4	353	511	3	174	242	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	12	more than 11000	123	28	0.34	0.69	0.13	0.56	340	405	2.3	122	47	IP
No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	11	more than 11000	261	65	1.5	1.40	0.8	0.6	186	191	3.8	421	608	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes	EPTB	No	Yes	12.6	less than 4000	154	12.8	0.58	2.20	1.3	0.9	974	201	2.6	117	731	IP
Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	No	10	4000-11000	363	15	0.5	2.02	1.16	0.86	120	151	3.13	142	53	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.5	more than 11000	254	190	14.3	1.70	0.9	0.8	300	48	1.98	90	172	IP
Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	7.4	4000-11000	103	40	1.3	5.85	3.19	2.66	318	51	1.75	42	21	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Disseminated	Yes	Yes	11	4000-11000	566	30	0.9	0.70	0.3	0.4	444	732	3.49	81	372	IP
No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	EPTB	No	Yes	9.2	4000-11000	179	30	0.7	5.80	3.3	2.5	179	204	2.89	107	61	IP
No	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Disseminated	Yes	Yes	10	4000-11000	260	35	0.9	0.96	0.4	0.5	153	302	2.4	114	126	CP
No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No	PTB	No	No	11	4000-11000	269	28	0.9	1.02	0.6	0.42	569	312	2	98	88	IP
No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	14	4000-11000	300	45	0.8	0.60	0.3	0.3	151	136	2.3	150	145	IP
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	Disseminated	No	Yes	10	4000-11000	325	35	0.9	0.57	0.3	0.27	83.5	254	2.8	60	70	IP
Yes	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Disseminated	No	Yes	7	more than 11000	260	35	1.1	4.95	3	1.95	391	339	2	117	140	IP
No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	13.9	4000-11000	289	22	0.8	1.30	0.8	0.5	159	166	3.86	109	64	CP
Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	8.6	less than 4000	177	28.2	0.92	4.05	1.2	2.8	1208	457	3.07	351	523	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.4	4000-11000	216	23	0.87	2.30	1.3	1	275	315	3.14	91	322	CP
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	9	4000-11000	321	27	0.92	2.80	1.2	1.6	312	260	3	62	44	IP
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	Yes	10.74	less than 4000	412	20	0.97	1.80	0.95	0.85	278	324	3.15	91	54	IP
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	9.9	4000-11000	246	18	1	1.50	0.8	0.7	312	348	2.9	80	67	CP
Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	PTB	Yes	Yes	8.7	4000-11000	148	55	1.7	2.40	1	1.4	313	289	2.7	85	93	IP
No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.2	4000-11000	221	45	1.3	1.80	0.9	0.9	167	185	2.4	67	48	IP
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	9.9	4000-11000	369	62	1.3	1.80	1	0.8	189	221	2.5	86	74	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.7	less than 4000	261	23.7	1.1	1.36	0.66	0.7	269	345	2.4	186	108	CP
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	9.9	4000-11000	204	42	0.96	2.20	0.8	1.4	319	212	3.2	118	75	IP
Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	8.97	4000-11000	346	61	1.6	2.88	1.88	1	204	175	2.6	88	95	IP
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	14.5	more than 11000	287	41	0.79	0.59	0.41	0.18	273.7	254	3.27	118	55	CP
Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	13.7	more than 11000	297	26.5	0.54	8.60	6.1	2.5	319	383	2.83	125	60	IP
Yes	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	Yes	12	4000-11000	333	18.5	0.64	1.89	1.15	0.74	1965	###	4.13	85	153	IP

ABPL_152	DILI negative	APL	32	M	1.74	174	70	23.12	No	No	No	No	None	No	none	No	No
ABPL_153	DILI negative	BPL	46	M	1.72	172	68	22.99	No	No	No	No	None	No	none	No	No
ABPL_154	DILI negative	BPL	36	M	1.76	176	68	21.95	No	No	No	No	None	No	none	No	No
ABPL_155	DILI negative	BPL	20	F	1.64	164	54	20.08	No	No	No	No	None	No	none	No	No
ABPL_156	DILI negative	BPL	65	F	1.63	163	50	18.82	No	No	No	No	Hypertension	No	none	No	No
ABPL_157	DILI negative	APL	28	M	1.75	175	57	18.61	No	No	No	No	None	No	none	No	No
ABPL_158	DILI negative	BPL	75	M	1.72	172	55	18.59	No	No	No	No	Hypertension	No	none	No	No
ABPL_159	DILI negative	BPL	37	M	1.74	174	60	19.82	No	No	No	No	None	No	none	No	No
ABPL_160	DILI negative	APL	29	M	1.64	164	48	17.85	No	No	No	No	None	No	none	No	No
ABPL_161	DILI negative	APL	63	M	1.71	171	55	18.81	No	No	No	No	None	No	none	No	No
ABPL_162	DILI negative	APL	32	F	1.68	168	50	17.72	No	No	No	No	None	No	none	No	No
ABPL_163	DILI negative	APL	37	M	1.74	174	56	18.50	No	No	No	No	None	No	none	No	No
ABPL_164	DILI negative	BPL	39	F	1.68	168	46	16.30	No	No	No	No	None	No	none	No	No
ABPL_165	DILI negative	BPL	40	M	1.75	175	64	20.90	No	No	No	No	None	No	none	No	No
ABPL_166	DILI negative	APL	55	F	1.64	162	50	18.59	No	No	No	No	Hypertension	No	none	No	No
ABPL_167	DILI negative	BPL	28	F	1.62	162	50	19.05	No	No	No	No	None	No	none	No	No
ABPL_168	DILI negative	BPL	28	M	1.76	176	58	18.72	No	No	No	No	None	No	none	No	No
ABPL_169	DILI negative	BPL	38	F	1.63	163	48	18.07	No	No	No	No	None	No	none	No	No
ABPL_170	DILI negative	APL	45	M	1.7	170	56	19.38	No	No	Yes	No	None	No	none	No	No
ABPL_171	DILI negative	BPL	39	F	1.62	162	47	17.91	No	No	No	No	None	No	none	No	No
ABPL_172	DILI negative	BPL	24	M	1.62	162	46	17.53	No	No	No	No	None	No	none	No	No
ABPL_173	DILI negative	BPL	63	M	1.68	168	55	19.49	No	No	No	No	None	No	none	No	No
ABPL_174	DILI negative	BPL	75	M	1.74	174	68	22.46	No	No	No	No	None	No	none	No	No
ABPL_175	DILI negative	BPL	25	F	1.63	163	50	18.82	No	No	No	No	None	No	none	No	No
ABPL_176	DILI negative	BPL	35	F	1.62	162	48	18.29	No	No	No	No	None	No	none	No	No
ABPL_177	DILI negative	BPL	55	M	1.74	174	62	20.48	No	No	No	No	Hypertension	No	none	No	No
ABPL_178	DILI negative	BPL	57	F	1.62	162	45	17.15	No	No	No	No	Hypertension	No	none	No	No
ABPL_179	DILI negative	APL	25	M	1.75	175	58	18.94	No	No	Yes	No	None	No	none	No	No
ABPL_180	DILI negative	BPL	30	M	1.72	172	55	18.59	No	No	Yes	No	None	No	none	No	No
ABPL_181	DILI negative	BPL	61	F	1.61	161	46	17.75	No	No	No	No	Diabetes	No	none	No	No
ABPL_182	DILI negative	BPL	38	M	1.72	172	51	17.24	No	No	Yes	No	None	No	none	No	No
ABPL_183	DILI negative	APL	34	F	1.65	165	47	17.26	No	No	No	No	None	No	none	No	No
ABPL_184	DILI negative	BPL	21	F	1.63	163	45	16.94	No	No	No	No	None	No	none	No	No
ABPL_185	DILI negative	BPL	32	M	1.74	174	62	20.48	No	No	Yes	No	None	No	none	No	No
ABPL_186	DILI negative	BPL	32	F	1.62	162	45	17.15	No	No	No	No	None	No	none	No	No
ABPL_187	DILI negative	APL	29	F	1.63	163	46	17.31	No	No	No	No	None	No	none	No	No
ABPL_188	DILI negative	BPL	60	M	1.74	174	55	18.17	No	No	Yes	No	Diabetes	No	none	No	No
ABPL_189	DILI negative	BPL	34	M	1.75	175	55	17.96	No	No	No	No	None	No	none	No	No
ABPL_190	DILI negative	BPL	66	M	1.76	176	62	20.02	No	No	No	No	Hypertension	No	none	No	No
ABPL_191	DILI negative	BPL	28	F	1.63	163	49	18.44	No	No	No	No	None	No	none	No	No
ABPL_192	DILI negative	APL	32	F	1.64	164	50	18.59	No	No	No	No	None	No	none	No	No
ABPL_193	DILI negative	APL	24	M	1.74	174	55	18.17	No	No	No	No	None	No	none	No	No
ABPL_194	DILI negative	BPL	20	F	1.64	164	52	19.33	No	No	No	No	None	No	none	No	No
ABPL_195	DILI negative	BPL	72	M	1.72	172	60	20.28	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_196	DILI negative	BPL	72	M	1.76	176	58	18.72	No	No	Yes	No	None	No	none	No	No
ABPL_197	DILI negative	BPL	30	M	1.74	174	56	18.50	No	No	Yes	No	None	No	none	No	No
ABPL_198	DILI negative	BPL	57	M	1.75	175	62	20.24	No	No	No	No	Hypertension	No	none	No	No
ABPL_199	DILI negative	BPL	25	F	1.62	162	46	17.53	No	No	No	No	None	No	none	No	No
ABPL_200	DILI negative	APL	22	M	1.76	1.76	57	18.40	No	No	No	No	None	No	none	No	No
ABPL_201	DILI negative	BPL	55	F	1.63	163	49	18.44	No	No	No	No	Hypertension	No	none	No	No
ABPL_202	DILI negative	APL	28	F	1.64	164	49	18.22	No	No	No	No	None	No	none	No	No
ABPL_203	DILI negative	BPL	57	M	1.74	174	58	19.16	No	No	Yes	No	Diabetes	No	none	No	No
ABPL_204	DILI negative	BPL	31	F	1.64	164	55	20.45	No	No	No	No	None	No	none	No	No
ABPL_205	DILI negative	BPL	88	M	1.74	174	60	19.82	No	No	No	No	Diabetes	No	none	No	No
ABPL_206	DILI negative	BPL	21	F	1.64	164	55	20.45	No	No	No	No	None	No	none	No	No
ABPL_207	DILI negative	BPL	21	F	1.65	165	45	16.53	No	No	No	No	None	No	none	No	No
ABPL_208	DILI negative	BPL	72	M	1.73	173	54	18.04	No	No	Yes	No	None	No	none	No	No
ABPL_209	DILI negative	BPL	58	M	1.76	176	59	19.05	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_210	DILI negative	APL	30	M	1.73	173	51	17.04	No	No	Yes	No	None	No	none	No	No
ABPL_211	DILI negative	APL	21	M	1.76	176	54	17.43	No	No	No	No	None	No	none	No	No
ABPL_212	DILI negative	BPL	55	F	1.64	164	52	19.33	No	No	No	No	Hypertension	No	none	No	No

No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	EPTB	No	Yes	13	4000-11000	328	20	0.6	0.80	0.2	0.6	32	35	3.5	25	30
Yes	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	14	4000-11000	225	16	0.4	0.90	0.4	0.5	35	32	4	30	37
No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	EPTB	Yes	Yes	13.2	4000-11000	377	25	0.9	1.00	0.2	0.8	33	30	3.8	33	28
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	Yes	12.9	4000-11000	352	17	0.9	0.70	0.2	0.5	40	38	3.9	33	31
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	12.5	4000-11000	197	32	1.1	0.90	0.7	0.2	33	38	3.6	40	35
No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	14	4000-11000	326	22	0.8	0.80	0.5	0.3	28	33	3.4	23	34
Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	12	4000-11000	178	33	1.1	1.00	0.5	0.5	55	75	3	44	37
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	13	4000-11000	200	29	1	1.40	0.9	0.5	52	50	3.5	41	44
Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	12	4000-11000	225	25	0.9	1.10	0.6	0.5	48	52	3.8	50	47
No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	14	4000-11000	375	28	0.7	0.70	0.4	0.3	45	40	3.36	36	41
No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	12.8	4000-11000	310	30	0.9	1.10	0.7	0.4	41	38	3.9	38	55
No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	EPTB	No	No	13	4000-11000	191	27	1	0.80	0.3	0.5	37	44	3.2	57	42
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	13.5	4000-11000	221	28	0.8	1.30	0.7	0.6	56	61	3.7	41	42
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	12.7	4000-11000	178	25	0.9	1.00	0.7	0.3	36	42	3.5	40	56
No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11.7	4000-11000	375	30	0.7	1.20	0.8	0.4	54	50	3.2	34	42
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.7	less than 4000	395	17	1	0.90	0.2	0.7	55	41	3	46	35
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	11.7	4000-11000	224	24	0.7	1.20	0.5	0.7	42	38	3.3	38	49
Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	12	4000-11000	374	12	0.8	1.10	0.7	0.4	41	38	3.5	40	38
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	13.7	4000-11000	320	34	1.2	1.60	0.9	0.7	45	55	3.8	38	42
No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11.3	4000-11000	231	27	1.1	1.80	0.9	0.9	50	55	2.8	44	47
No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	EPTB	No	No	12.3	4000-11000	375	28	0.9	1.10	0.7	0.4	38	47	3.3	47	36
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	13	4000-11000	246	36	0.7	1.00	0.8	0.2	49	52	3.8	43	46
No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	Yes	12.9	4000-11000	325	36	0.8	1.30	0.8	0.5	49	53	3.7	55	52
Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	11.7	4000-11000	278	34	0.97	1.10	0.8	0.3	44	40	3.8	43	57
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.9	4000-11000	300	27	1.2	0.70	0.5	0.2	42	38	3.6	45	56
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11	4000-11000	214	36	1.1	1.30	0.8	0.5	46	53	4.3	53	62
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	Yes	Yes	10.6	4000-11000	276	38	1.3	1.50	0.9	0.6	39	51	3.7	60	55
No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10	4000-11000	187	34	0.67	1.70	0.8	0.9	45	47	3.2	56	45
No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	EPTB	No	Yes	12.3	4000-11000	254	27	1	1.60	0.7	0.9	41	37	3.4	31	54
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10.5	4000-11000	371	45	0.88	1.60	0.9	0.7	48	57	2.7	49	43
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	Yes	13.7	4000-11000	212	39	1.3	1.70	0.8	0.9	28	31	3.2	43	36
Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	13.5	4000-11000	258	32	0.79	1.10	0.5	0.6	38	47	3.4	51	48
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	11.9	4000-11000	327	30	1.09	1.30	0.9	0.4	46	38	3.78	43	47
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	Yes	Yes	12.3	4000-11000	425	29	1.1	1.40	0.8	0.6	34	37	3.2	51	43
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	Yes	10.4	4000-11000	352	36	0.69	0.70	0.35	0.35	35	40	2.97	43	47
No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	Yes	11.3	4000-11000	239	27	1.2	1.50	0.7	0.8	48	49	3.8	49	53
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	Yes	12.2	4000-11000	298	22	0.69	1.30	0.7	0.6	38	31	3.2	34	38
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	11.4	4000-11000	310	23	0.98	1.10	0.75	0.35	58	44	3	52	43
Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	12.9	4000-11000	289	18	1.4	1.80	0.8	1	56	61	3.7	47	51
No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	EPTB	No	Yes	13.4	4000-11000	367	29	1.3	1.40	0.9	0.5	57	54	3.6	49	52
Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	No	11.8	4000-11000	320	26	1	1.40	0.9	0.5	31	33	3.8	33	38
No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	No	12.3	4000-11000	167	34	1.1	1.30	0.6	0.7	54	47	3.4	39	54
Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	11.7	4000-11000	296	32	0.78	0.88	0.35	0.53	41	32	3.4	38	37
Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	10.6	4000-11000	237	42	1.3	0.90	0.35	0.55	36	41	3.7	38	47
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	Yes	11.3	4000-11000	367	37	1.4	1.70	0.9	0.8	37	40	3.2	42	46
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	12.4	4000-11000	392	24	0.76	1.44	0.88	0.64	36	42	3.4	39	43
No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	EPTB	No	Yes	11.6	4000-11000	229	28	1.4	1.38	0.9	0.48	54	68	3.4	52	56
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.6	4000-11000	163	21	0.93	0.67	0.41	0.26	38	52	3.1	55	54
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	11	4000-11000	361	29	0.86	1.40	0.8	0.6	38	43	3.3	38	42
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	10.7	4000-11000	220	34	0.73	1.20	0.8	0.4	45	50	3.4	51	53
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	12.7	4000-11000	298	36	0.98	1.50	0.9	0.6	38	33	3.2	40	38
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11.4	4000-11000	189	24	1	1.40	0.6	0.8	42	37	3.6	37	41
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.3	4000-11000	276	17	0.7	0.86	0.53	0.33	36	32	3.4	38	36
Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	Yes	Yes	9.9	4000-11000	188	17	0.99	0.96	0.63	33	47	56	3.7	56	58
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11	4000-11000	346	38	0.85	1.30	0.6	0.7	42	38	3.5	33	48
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	EPTB	No	Yes	10.7	4000-11000	278	19	0.98	0.76	0.33	0.43	52	54	3.8	45	53
Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	10.3	4000-11000	273	16	1.1	1.50	0.8	0.7	49	44	3.6	38	42
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11.4	4000-11000	196	25	0.98	1.00	0.7	0.3	41	52	3.1	51	54
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	12.7	4000-11000	352	21	0.89	0.97	0.55	0.42	36	43	4.1	37	31
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	PTB	No	No	11	4000-11000	294	14	1.19	1.69	0.69	1	32	48	3.1	57	38
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.4	more than 11000	164	19	0.86	1.39	0.79	0.6	57	45	2.9	49	57

ABPL_213	DILI negative	BPL	71	M	1.73	173	56	18.71	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_214	DILI negative	APL	30	M	1.75	175	52	16.98	No	No	Yes	No	None	No	none	No	No
ABPL_215	DILI negative	BPL	74	M	1.75	175	56	18.29	No	No	Yes	No	Diabetes	No	none	No	No
ABPL_216	DILI negative	APL	47	M	1.74	174	62	20.48	No	No	Yes	No	None	No	none	No	No
ABPL_217	DILI negative	APL	32	F	1.66	166	52	18.87	No	No	No	No	None	No	none	No	No
ABPL_218	DILI negative	APL	24	F	1.65	165	51	18.73	No	No	No	No	None	No	none	No	No
ABPL_219	DILI negative	APL	24	F	1.65	165	54	19.83	No	No	No	No	None	No	none	No	No
ABPL_220	DILI negative	BPL	19	M	1.75	175	53	17.31	No	No	No	No	None	No	none	No	No
ABPL_221	DILI negative	BPL	31	M	1.74	174	58	19.16	No	No	Yes	No	None	No	none	No	No
ABPL_222	DILI negative	BPL	59	M	1.72	172	58	19.61	No	No	Yes	No	None	No	none	No	No
ABPL_223	DILI negative	APL	60	F	1.64	164	49	18.22	No	No	No	No	Diabetes	No	none	No	No
ABPL_224	DILI negative	BPL	29	M	1.72	172	52	17.58	No	No	Yes	No	None	No	none	No	No
ABPL_225	DILI negative	BPL	41	F	1.63	163	51	19.20	No	No	No	No	None	No	none	No	No
ABPL_226	DILI negative	APL	28	M	1.74	174	56	18.50	No	No	Yes	No	None	No	none	No	No
ABPL_227	DILI negative	BPL	25	M	1.75	175	58	18.94	No	No	Yes	No	None	No	none	No	No
ABPL_228	DILI negative	APL	22	F	1.65	165	50	18.37	No	No	No	No	None	No	none	No	No
ABPL_229	DILI negative	BPL	30	M	1.75	175	59	19.27	No	No	Yes	No	None	No	none	No	No
ABPL_230	DILI negative	BPL	63	M	1.74	174	53	17.51	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_231	DILI negative	APL	68	M	1.76	176	62	20.02	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_232	DILI negative	APL	64	M	1.76	176	70	22.60	No	No	Yes	No	Diabetes	No	none	No	No
ABPL_233	DILI negative	BPL	46	F	1.64	154	52	19.33	No	No	No	No	None	No	none	No	No
ABPL_234	DILI negative	BPL	51	F	1.63	163	52	19.57	No	No	No	No	Hypertension	No	none	No	No
ABPL_235	DILI negative	BPL	23	F	1.63	163	48	18.07	No	No	No	No	None	No	none	No	No
ABPL_236	DILI negative	BPL	37	M	1.76	176	57	18.40	No	No	Yes	No	None	No	none	No	No
ABPL_237	DILI negative	BPL	35	M	1.76	176	66	21.31	No	No	Yes	No	None	No	none	No	No
ABPL_238	DILI negative	APL	38	F	1.63	163	50	18.82	No	No	No	No	None	No	none	No	No
ABPL_239	DILI negative	BPL	37	F	1.62	162	48	18.29	No	No	No	No	None	No	none	No	No
ABPL_240	DILI negative	BPL	47	M	1.74	175	58	19.16	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_241	DILI negative	BPL	35	F	1.62	162	47	17.91	No	No	No	No	None	No	none	No	No
ABPL_242	DILI negative	BPL	32	M	1.75	175	59	19.27	No	No	Yes	No	None	No	none	No	No
ABPL_243	DILI negative	BPL	71	M	1.73	173	59	19.71	No	No	Yes	No	Diabetes	No	none	No	No
ABPL_244	DILI negative	BPL	49	M	1.75	175	64	20.90	No	No	No	No	Hypertension	No	none	No	No
ABPL_245	DILI negative	BPL	59	M	1.74	174	68	22.46	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_246	DILI negative	APL	40	M	1.75	175	67	21.88	No	No	Yes	No	None	No	none	No	No
ABPL_247	DILI negative	BPL	44	F	1.63	163	52	19.57	No	No	No	No	None	No	none	No	No
ABPL_248	DILI negative	BPL	28	F	1.66	166	50	18.14	No	No	No	No	None	No	none	No	No
ABPL_249	DILI negative	APL	47	M	1.74	174	66	21.80	No	No	Yes	No	None	No	none	No	No
ABPL_250	DILI negative	BPL	37	M	1.75	175	70	22.86	No	No	Yes	No	None	No	none	No	No
ABPL_251	DILI negative	APL	24	F	1.62	162	52	19.81	No	No	No	No	None	No	none	No	No
ABPL_252	DILI negative	APL	19	F	1.64	164	50	18.59	No	No	No	No	None	No	none	No	No
ABPL_253	DILI negative	BPL	59	F	1.63	163	51	19.20	No	No	No	No	Hypertension	No	none	No	No
ABPL_254	DILI negative	APL	28	F	1.62	162	49	18.67	No	No	No	No	None	No	none	No	No
ABPL_255	DILI negative	BPL	46	F	1.63	163	52	19.57	No	No	No	No	None	No	none	No	No
ABPL_256	DILI negative	APL	20	F	1.65	165	51	18.73	No	No	No	No	None	No	none	No	No
ABPL_257	DILI negative	APL	36	F	1.64	164	49	18.22	No	No	No	No	None	No	none	No	No
ABPL_258	DILI negative	BPL	21	F	1.66	166	55	19.96	No	No	No	No	None	No	none	No	No
ABPL_259	DILI negative	APL	23	F	1.65	165	53	19.47	No	No	No	No	None	No	none	No	No
ABPL_260	DILI negative	APL	50	M	1.73	173	58	19.38	No	No	Yes	No	Hypertension	No	none	No	No
ABPL_261	DILI negative	BPL	19	M	1.74	174	66	21.80	No	No	No	No	None	No	none	No	No
ABPL_262	DILI negative	BPL	35	F	1.62	162	52	19.81	No	No	No	No	None	No	none	No	No
ABPL_263	DILI negative	APL	61	F	1.63	163	55	20.70	No	No	No	No	Diabetes	No	none	No	No
ABPL_264	DILI negative	BPL	23	M	1.7	170	54	18.69	No	No	No	No	None	No	none	No	No
ABPL_265	DILI negative	APL	76	M	1.72	172	58	19.61	No	No	No	No	Hypertension	No	none	No	No
ABPL_266	DILI negative	BPL	35	F	1.61	161	43	16.59	No	No	No	No	None	No	none	No	No
ABPL_267	DILI negative	BPL	46	F	1.6	160	52	20.31	No	No	No	No	None	No	none	No	No
ABPL_268	DILI negative	BPL	49	F	1.62	162	48	18.29	No	No	No	No	Hypertension	No	none	No	No
ABPL_269	DILI negative	BPL	27	M	1.7	170	46	15.92	No	No	No	No	None	No	none	No	No
ABPL_270	DILI negative	BPL	26	M	1.74	174	70	23.12	No	No	No	No	None	No	none	No	No
ABPL_271	DILI negative	APL	23	F	1.61	161	49	18.90	No	No	No	No	None	Yes	none	No	No

Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10	4000-11000	199	36	1.3	1.56	1	0.56	43	48	3.2	47	49	
Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Disseminated	No	Yes	9.89	4000-11000	183	33	1.23	1.44	0.77	0.67	56	51	2.87	52	55	
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	10.21	4000-11000	361	18.7	0.96	1.50	0.8	0.7	42	49	3.4	25	49	
Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	EPTB	No	Yes	10.51	4000-11000	329	36.78	0.92	1.36	0.76	0.6	54	58	3.4	46	51	
No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	EPTB	No	Yes	11.7	4000-11000	236	28.47	1	1.63	0.9	0.73	55	42	3.21	49	42	
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11.96	4000-11000	394	38	0.87	1.52	0.9	0.62	46	51	3.69	43	54	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10.64	4000-11000	369	19.51	0.92	1.32	0.72	0.6	52	43	3.7	39	42	
No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	EPTB	No	No	11.4	4000-11000	362	35	1.12	1.25	0.65	0.6	31	48	3.96	32	47	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10	4000-11000	362	28	0.85	1.00	0.6	0.4	36	42	2.89	52	43	
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	9.6	less than 4000	146	43	1.4	1.56	0.9	0.66	51	54	3.22	52	43	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	9.75	4000-11000	153	17	1.1	1.22	0.61	0.6	18	23	3.1	35	34	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	Yes	Yes	11.2	4000-11000	214	24	1.12	1.42	0.82	0.6	43	52	3.4	33	21	
Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.2	4000-11000	210	21	0.78	0.80	0.3	0.5	32	42	2.84	33	29	
No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.2	4000-11000	375	25.6	0.76	0.85	0.65	0.2	31	28	3.41	28	37	
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	12.7	4000-11000	398	23	1.2	1.32	0.042	0.09	27	38	3.1	25	34	
No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	9.34	4000-11000	193	32	1.06	1.34	0	0.44	32	35	3.15	25	31	
Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	9.54	4000-11000	283	34	1.24	1.60	0.7	0.9	24	30	3.4	38	42	
Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Disseminated	No	Yes	10.5	4000-11000	411	34	1.3	1.22	0.61	0.61	52	36	2.8	42	34	
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	8.9	4000-11000	326	21	1.2	1.72	0.9	0.82	54	56	2.78	52	43	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	12.6	4000-11000	241	42	1.52	1.92	0.92	1	38	45	3.4	41	49	
No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.7	4000-11000	216	28	0.86	1.42	0.62	0.8	51	46	2.95	49	54	
No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	11.2	4000-11000	385	21	0.85	1.28	0.38	0.9	31	34	3.2	52	37	
Yes	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Disseminated	No	Yes	9.2	4000-11000	365	18	0.89	1.15	0.55	0.6	42	37	3.1	33	42	
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	10.2	4000-11000	326	19	1.1	1.29	0.69	0.6	43	35	2.75	32	35	
No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	11.7	4000-11000	289	29	0.97	1.30	0.9	0.4	53	47	3	52	68	
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	9.1	4000-11000	354	28	1.2	1.47	0.77	0.7	57	52	3.2	41	48	
Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	EPTB	No	Yes	10.1	4000-11000	374	17.98	1.14	1.24	0.64	0.6	47	39	2.98	36	41	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11.96	more than 11000	251	18.3	1.2	1.42	0.42	1	42	4	2.87	55	51	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	Yes	Yes	10.47	4000-11000	157	23	1.34	1.75	0.95	0.8	39	43	3.1	43	38	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	9.7	4000-11000	142	23	1.2	1.33	0.73	0.6	43	49	3.2	41	45	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	10.54	4000-11000	237	21	1	1.45	0.9	0.55	37	42	3.4	43	54	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11	4000-11000	385	28	0.98	1.32	0.42	0.9	55	57	3	45	57	
Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	No	10	4000-11000	394	34	1.1	1.34	0.9	0.44	48	41	3.12	52	51	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	13	4000-11000	274	34	0.9	1.28	0.6	68	42	43	3.4	38	42	
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.23	4000-11000	368	18.32	1.1	1.30	0.6	0.7	46	48	3.1	54	49	
Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	No	9.7	4000-11000	241	26	1.2	1.45	0.8	0.65	47	49	3.4	42	40	
No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	Yes	Yes	10.2	4000-11000	352	27	1.01	1.14	0.7	0.44	51	54	3.12	48	36	
Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	EPTB	Yes	Yes	11	4000-11000	237	23	1	1.20	0.6	0.6	48	42	3.2	42	38	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	Yes	10.1	4000-11000	300	17.98	1.2	1.40	0.6	0.8	42	40	3	44	38	
Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	11	4000-11000	238	18	1.1	1.30	0.7	0.6	39	42	3.2	41	44	
No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	10.8	4000-11000	314	19.7	1	1.40	0.8	0.6	38	40	3.1	50	48	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	Yes	Yes	9.7	4000-11000	243	23	1.1	1.20	0.45	0.75	49	51	3.7	52	43	
Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	EPTB	No	Yes	10.4	less than 4000	368	22	1.2	1.30	0.7	0.6	47	48	3.6	51	52	
Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	EPTB	No	Yes	11.8	4000-11000	173	18	0.88	1.35	0.9	0.45	43	47	3.2	50	47	
Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	Disseminated	No	Yes	9.8	4000-11000	367	20.7	0.76	0.98	0.66	0.32	42	55	2.7	48	45	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	No	No	9.8	4000-11000	326	21	0.98	1.12	0.72	0.4	37	48	3.2	40	46	
No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	EPTB	No	Yes	11	4000-11000	315	16	1.1	1.24	0.6	0.64	45	48	3.21	43	46	
Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	Yes	12	4000-11000	382	36	1.4	1.60	0.7	0.9	53	52	2.85	53	52	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	EPTB	No	Yes	12	4000-11000	257	28	1.3	1.69	0.69	1	58	42	3.2	54	59	
Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	EPTB	No	Yes	12.9	4000-11000	349	24	1.2	1.50	0.78	0.72	59	67	3.4	29	31	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	PTB	Yes	No	11.7	4000-11000	174	23	0.98	1.27	0.66	0.61	66	58	3.8	38	49	
No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	EPTB	No	Yes	12	4000-11000	241	14	0.98	1.33	0.7	0.63	51	44	3.7	44	52	
Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	No	13	4000-11000	365	38	1.3	1.80	0.8	1	42	49	3.2	41	50	
Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	Disseminated	No	Yes	11.7	4000-11000	298	24	1.2	0.96	0.66	0.3	36	48	3.15	31	29	
No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	EPTB	No	Yes	11.56	4000-11000	326	21	0.86	1.33	0.7	0.63	33	28	3.49	40	30	
Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	PTB	No	Yes	10.3	4000-11000	221	16	0.6	1.50	0.8	0.7	52	51	3.4	28	46	
Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Disseminated	No	Yes	11	4000-11000	358	19	0.98	1.80	0.8	1	43	47	3.5	52	36	
No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	No	13	4000-11000	372	27	0.94	1.40	0.8	0.6	54	48	3.4	53	51	
No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	EPTB	No	No	13.4	4000-11000	207	17.6	0.96	1.10	0.75	0.35	47	39	3.5	41	46	